

SELECT COMMITTEE ON
SCIENCE AND TECHNOLOGY

RESISTANCE TO ANTIBIOTICS
AND OTHER ANTIMICROBIAL AGENTS

EVIDENCE

Ordered to be printed 17th March 1998

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CALL FOR EVIDENCE
Issued 14th 1997

The Science and Technology Committee of the House of Lords has appointed a Sub-Committee, chaired by Lord Sainsbury of Staffordshire (formerly Professor of Tropical Pathology, University of Cambridge), to conduct an inquiry into the growing resistance to antibiotics and other antimicrobial agents, and its implications for UK and international public health. The Sub-Committee will report to the House of Lords, with recommendations addressed to the Government, in 1998.

The Sub-Committee invites written submissions on any aspect of this topic, and in particular:

- (i) Bacterial resistance to antibiotics, particularly in hospital infections and in the community.
- (ii) Prescription and use of antibiotics, including in the home.
- (iii) The future of antibiotics: drug design and molecular biology. Prospects for vaccination.
- (iv) The roles of Government, the NHS, the Public Health Laboratory Service, the pharmaceutical industry, the research community, the EU and the World Health Organisation.

The Sub-Committee will also consider resistance to vaccines and antifolate drugs, as well as parasitic and protozoan infections, and resistance to anti-viral agents.

The Sub-Committee will also consider resistance to pesticides and herbicides, and the use of antibiotics in agriculture, and the potential for resistance to these agents. The Sub-Committee will also consider the use of antibiotics in the environment, and the potential for resistance to these agents. The Sub-Committee will also consider the use of antibiotics in the environment, and the potential for resistance to these agents.

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ORAL AND WRITTEN EVIDENCE

Association of Medical Microbiologists
Written Evidence
Oral Evidence, 14 October 1997
Supplementary Written Evidence—see page 174

Public Health Laboratory Service (PHLS)
Written Evidence

British Society for Antimicrobial Chemotherapy (BSAC)
Written Evidence

PHLS and BSAC
Oral Evidence, 21 October 1997

Ordered to be printed 17th March 1998

World Health Organisation (WHO)
Written Evidence
Oral Evidence, 12 November 1997
Supplementary Written Evidence—see page 174

The Stationery Office
Written Evidence
Oral Evidence, 26 October 1997

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INFORMATION SERVICE
Xpca
Houll
13 MAY 1998
Wellcome Centre for Medical Science

Drug resistance
in microorganisms 12709

CALL FOR EVIDENCE

Issued July 1997

The Science and Technology Committee of the House of Lords has appointed Sub-Committee I, chaired by Lord Soulsby of Swaffham Prior (Emeritus Professor of Animal Pathology, University of Cambridge), to conduct an inquiry into the rise in resistance to antibiotics and other antimicrobial agents, and its implications for UK and international public policy. The Committee will produce a report to the House of Lords, with recommendations addressed to the Government, early in 1998.

The Sub-Committee invites written submissions on any aspect of this topic, and in particular:

- (i) Bacteria resistant to antibiotics: eg TB, pneumonia, meningitis, salmonella, gonorrhoea and hospital infections including MRSA. Extent and trends; surveillance; infection control.
- (ii) Prescription and use of antibiotics; social/ethnic factors.
- (iii) The future of antibiotics: drug design and molecular strategy. Prospects for vaccination.
- (iv) The roles of Government, the NHS, the Public Health Laboratory Service, the pharmaceutical industry, the research community, the EU and the World Health Organisation.

The Sub-Committee will also consider resistant protozoan and metazoan organisms, eg malarial parasites and parasitic nematodes; and resistance to anti-viral agents.

The Sub-Committee is aware of the issues surrounding the use of antibiotics as growth promoters, and for prophylactic and therapeutic purposes, in animals and fish, and the use of antibiotic resistant markers in genetically modified organisms. The former is currently under consideration by the Government's Advisory Committee on the Microbiological Safety of Food, and the latter has recently been considered by the Advisory Committee on Novel Foods and Processes. Therefore these questions are not the main focus of this inquiry.

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MINUTES OF EVIDENCE

TAKEN BEFORE THE SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY
(SUB-COMMITTEE I)

TUESDAY 14 OCTOBER 1997

Present:

Dixon-Smith, L.	Rea, L.
Gregson, L.	Soulsby of Swaffham Prior, L.
Jenkin of Roding, L.	(Chairman)
McFarlane of Llandaff, B.	Walton of Detchant, L.
Masham of Ilton, B.	Winston, L.
Perry of Walton, L.	
Platt of Writtle, B.	Phillips of Ellesmere, L.
Porter of Luddenham, L.	

Memorandum by The Association of Medical Microbiologists

Presented on its behalf by Professor David Reeves (Bristol), President and members of the Executive Committee:

Dr Michael Barnham (Harrogate), Dr Adrian Bint (Newcastle), Dr Graeme Calver (Maidstone), Professor Mike Emmerson (Nottingham), Dr Harold Gaya (London), Dr Mark Hastings (Birmingham), Dr Michael Kelsey (London), Dr John Kurtz (Oxford), Dr Neeta Manek (Stoke on Trent), Dr Ann Pallett (Southampton), Dr Judith Richards (Norwich), Professor Colin Roberts (London), Dr Richard Slack (Nottingham), Dr David Tompkins (Leeds), Dr Paul Wright (Hastings).

STRUCTURE OF THE EVIDENCE

This evidence is in three main parts:

1. The scientific and clinical basis of resistance
 - 1.1 Basis of antimicrobial action
 - 1.2 Basis of resistance
 - 1.3 The epidemiology of resistance
 - 1.4 The clinical impact of resistance
2. The current role of medical microbiology in the UK in detecting and controlling resistance
 - 2.1 The structure of microbiology and infection control services (and Table 1)
 - 2.2 The role of the medical microbiologist
 - 2.3 Pressures on microbiology and infection control services
3. Future actions to combat resistance
 - 3.1 Antibacterial usage
 - 3.2 Actions to improve the usage of antibacterials
 - 3.3 Providing new antibacterials
 - 3.4 Prioritising the actions (and Table 2)

Acknowledgements

Bibliography

Figure 1

Appendix 1A, 1B, 1C

Glossary and Abbreviations (7 pages)

In presenting this evidence the number of literature citations has been kept to a minimum. The view was taken that the Sub-Committee would already have access to those supporting uncontroversial statements, and that when opinion is given published evidence to support it does not exist or is scanty.

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The Association is uncomfortable about the linguistic inexactitude of using "antibiotic", "antimicrobial" and "antibacterial" as both nouns and adjectives, but hopes that the Sub-Committee will understand its wish to use the most concise language.

INTRODUCTION

For the purpose of this evidence *antimicrobial* is defined as a drug which exerts an action against microbial pathogens at low concentration and exhibits selective toxicity towards them *vis-à-vis* humans and animals, in distinction to disinfectants or antiseptics. Antimicrobials may be applied systematically (i.e., usually mouth or injection) or locally.

Although antimicrobials include agents active against viruses, fungi, protozoa and helminths as well as bacteria, this evidence will focus almost entirely on antibacterial agents. It is acknowledged that resistance to other agents is extremely important, especially in a world-wide context, but it is assumed that the major concern of the Select Committee will be for the UK.

Throughout the world bacterial resistance is rising inexorably, is causing major public concern, and is of direct relevant to the large majority of antimicrobial treatments. Thus no apology is necessary for using the space available for discussing almost exclusively antibacterial resistance.

The Association of Medical Microbiologists (AMM) will largely deal with topics (i) and (ii) in the Call for Evidence. The Association is described in an attachment. Our members include most of the medical microbiologists in practice in the UK. Many of them are members of other scientific societies (such as the BSAC and HIS) which make up the Federation of Infection Societies.

The different rates of resistance to antibiotics i.e., the prevalence amongst bacteria in different communities depends on antibiotic consumption and the rate of spread (cross-infection) between individuals. Some genera of microbes e.g., *Escherichia* and *Salmonella* are both easily passed between animals, including humans, and easily acquire resistance to antimicrobials when exposed. In contrast other micro-organisms, such as *Treponema pallidum* (the cause of syphilis), do not have these characteristics. The means to control acquired resistance in bacteria will vary with different situations but basically involves optimising antibacterial use and preventing infection as far as possible. Our members are closely involved in both these actions.

1. THE SCIENTIFIC AND CLINICAL BASIS OF RESISTANCE

1.1 Basis of antibacterial action

Antibacterial drugs given by mouth or injection to treat an infection circulate in the body's tissues and have access to cells of the human as well as the invading bacteria. The drugs must therefore exert *selective toxicity* i.e., produce a toxic effect on the bacteria but little or no harm to the human host.

In order to do this it is necessary to exploit differences in the composition of bacterial and human cells. For example, bacterial cells have an outer cell wall which is not present in human cells and some antibacterials act by interfering with the synthesis of the cell wall. Other act selectively on bacterial cells because they have a higher affinity for their enzymes than for the analogous human enzymes.

Most antibiotics have to get into the bacterial cell in order to act but various components of the outer bacterial envelope (which is made up of cell membranes and the cell wall) may restrict access. Some bacteria (called Gram-negative, which includes *E.coli* and *salmonella*) have an outer membrane which prevents the effective penetration of some antibacterials. Those antibacterials which are inactive against Gram-negative bacteria are generally effective against Gram-positive bacteria which differ from Gram-negatives in their cell envelope composition. This introduces the concept of *inherent resistance*, which is resistance exhibited to an antibacterial agent by all members of a bacterial species (e.g., *E.coli*). This is in contrast to *acquired resistance*, in which only some members of a species are resistant, usually by a specific mechanism such as producing an enzyme to destroy the drug, as occurs with penicillin.

In hospitals where sick people congregate and antibiotics are used intensively, strains of bacteria with inherent resistance, but which may not be particularly harmful in normal situations, can have a selective advantage and give rise to a change in the type and pattern of bacterial infections.

1.2 Basis of resistance

1.2.1 Resistance of a bacterium to antibacterials may be inherent for a number of reasons such as:

- the antibacterial cannot get into the bacterial cell;
- the antibacterial cannot attach itself to its site of action (target site);
- the target site is not present in the bacterial cell.

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1.2.2 Resistance may be *acquired* by a number of mechanisms:

- the modification or destruction of the antibacterial by enzymes;
- reduced ability of the antibacterial to pass through the cell envelope;
- reduced affinity of the target site for the antibacterial;
- expulsion of the antibacterial from the bacterial cell;
- the production of an analogue of the target site which is not sensitive to the antibacterial.

Sometimes two or more mechanisms exist simultaneously and combine to produce a greater degree of resistance.

1.2.3 There is a *genetic basis* for all resistance. Inherent resistance is determined by the genetic make-up typical for a particular bacterial species. Acquired resistance is brought about either by *mutation of the DNA* of the bacterial chromosome or by the *acquisition of DNA* containing a gene or genes which code for resistance.

1.2.3.1 *Mutations of the chromosomal DNA* occur naturally during bacterial multiplication. Most mutations conferring antibacterial resistance do not hold any special advantage for the bacteria unless the antibacterial is present. Indeed, normal biochemical processes within the bacteria may be subverted by the presence of a resistance gene, thus leading to “weaker” bacterial cells, which only have a selective advantage in the presence of the appropriate antibacterial. When the antibacterial is there however, bacteria which are sensitive to it are killed or inhibited from growing leaving an ecological niche in which the resistant bacteria thrive. Since bacteria can multiply rapidly (maximally every 20 minutes in vitro under ideal laboratory conditions, but generally slower in the human host) a resistant population can be quickly selected.

1.2.3.2 *Acquisition of DNA* is usually by movement of pieces of DNA called plasmids. Plasmids are separate from the chromosome and can replicate independently of it (i.e., at times other than cell division). Plasmids coding antibacterial resistance (called R-plasmids) may carry determinants for resistance to not just one but many antibacterials. In this way resistances can become linked even though they are brought about by entirely different mechanisms. The ability of a plasmid to replicate itself independently of the chromosome is also an important property since a bacterial cell may contain several “copies” of a bacterial resistance gene. This may produce a higher level of resistance to the antibacterial, and the ability to transfer resistance to other bacterial cells, without losing the characteristic itself.

DNA may be transmitted to other bacterial cells by three processes:

- conjugation
- transformation
- transduction

Conjugation is the most common process for resistance genes and occurs when DNA passes along a tube which links two bacteria. Conjugation takes place readily between bacteria of the same species but can also occur between bacteria of similar species, albeit less efficiently. Thus a resistance can be transferred from one species to another.

Transformation can occur when DNA is released from a dead bacterium and is absorbed by a living one. Not many bacterial species are susceptible to transformation but an important feature as far as resistance is concerned is that the DNA acquired by this process may come from a species unrelated to the recipient, and antibacterial resistance may be acquired even from species not usually responsible for causing disease.

These first two mechanisms may result in the spread of resistance genes to species other than those from which they first evolved, something which would not be possible in direct descendants inheriting characteristics from chromosomal DNA.

Transduction, which is the carriage of bacterial DNA on a virus which infects and replicates in bacterial cells (bacteriophage) is less commonly involved in transferable antibacterial resistance.

Transposons are pieces of DNA which can be transferred readily between the chromosome and plasmid. They are also known as “jumping genes” and resistance genes may exist as part of transposons. They are important because they confer genetic flexibility to bacteria enabling resistance genes to evolve and disseminate amongst bacteria.

The message that emerges from this brief exposition of the genetics of resistance is that mechanisms exist in bacteria to facilitate their long term population survival in the face of continuing assault by antibacterials. Resistance, once encoded in genes, can spread rapidly within the population of a species and even to other types of bacteria.

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1.2.3.3 In clinical laboratory practice resistance is almost always determined by assessing how bacteria respond when exposed in the laboratory to the antibacterial drug. This is sometimes termed *in vitro* resistance. Although this is clearly removed from conditions in the patient it is currently the best surrogate we have for determining the likely outcome of antibacterial therapy. For clinical purposes sensitivity (or susceptibility, as it is sometimes termed), that is the obverse of resistance, is usually determined in one of two ways. The first entails growing a "lawn" of bacteria on a plate of nutrient agar (jelly-like) medium and determining the size of a zone of inhibition of bacterial growth around an antibacterial-containing paper disc placed on the "lawn". The second involves producing a set of growth medium containing a series of incrementally decreasing concentrations of antibacterial drug, growing the bacterial strain in the medium, and determining the lowest concentration of drug which prevents the bacteria from growing. This concentration is termed the *minimal inhibitory concentration* (MIC).

Various degrees of *in vitro* resistance can be observed. *Minimal resistance* might not be detected at all, particularly by the rather crude routine test using antibiotic-impregnated paper discs. Some laboratories use the term *moderately resistant* to denote resistance where the bacteria is not as great as full resistance and which might respond to a large dosage of antibacterial. The term *resistant* is usually taken to mean a degree of resistance at which therapy is likely to fail when the infection is treated with the usual or even larger than usual dosage.

1.2.3.4 Another level at which resistance can be viewed is termed *clinical resistance*. In other words, does *in vitro* resistance translate into the therapeutic situation? Just because a bacterial strain is "resistant" *in vitro* does not mean that therapy will always fail and neither does a report of *sensitive* (i.e., not resistant) mean that therapy will always succeed. The body's natural defence mechanisms are a vital part of combating infection and antibacterial therapy is often just an adjunct to them. Thus, patients often recovered from bacterial infection before the advent of antibiotics and they still often do even when untreated. Conversely, patients with impaired natural defence mechanisms (for example, those immunosuppressed to prevent organ transplant rejection, or those with low number of white cells in their blood) may not respond to appropriate antibacterial therapy (i.e., a normally sufficient dosage of antibacterial to which the invading bacteria are sensitive *in vitro*).

It should also be remembered that the concentrations of antibacterial in a patient vary between body sites. When an antibacterial is given orally or by injection it is found in and distributed to the remainder of the body by the blood. Only limited penetration from the blood is achieved to some sites such as the cerebrospinal fluid and the brain. On the other hand, many antibacterials achieve concentrations in the urine much higher than those in the blood. Thus therapy may succeed or fail depending on the site of infection, and a minimal degree of resistance may not be relevant in one site while it is crucial in another. The general aim of antibacterial therapy is to ensure as far as possible that the concentration of the antibacterial at the site of infection exceeds the lowest concentration which will inhibit the growth of the bacteria *in vitro*, preferably by 2- to 8-fold.

There are few published examples of correlation between *in vitro* resistance and clinical failure of therapy. The reasons for this are, first that doctors tailor empirical therapy to have a good chance of the presumptive infection being sensitive *in vitro* to the agents chosen. Second, antibacterials are given in dosages which are far greater than strictly necessary to cure most infections so as to have a margin of safety. It is only when therapy has to be minimalistic, such as in the single-dose treatment of gonorrhoea (Figure 1), that the effect of *in vitro* resistance is clearly shown.

1.3 The epidemiology of resistance

1.3.1 There are two major reasons to collect data about antibacterial resistance:

- (a) to identify pathogens with new resistances e.g., VRMRSA, penicillin-resistant meningococci.
- (b) to quantify the rate of antibacterial resistance in a particular community, e.g., the number of MRSA isolates in a hospital, or the percentage of ampicillin-resistant *E.coli* in urine samples sent by GPs.

The systematic collection and analysis of data, the inferences drawn from them, and feedback to those providing them is *surveillance*. For infectious diseases information is collected on certain notifiable diseases (under the Public Health Act 1984 and Infectious Diseases Regulations 1988) and by the clinician seeing the patient notifying them to the "Proper Officer", usually the Consultant for Communicable Disease Control (CCDC) of the Health Authority. Laboratory reporting to Communicable Disease Surveillance Centre/PHLS is at present voluntary. Antibacterial resistance is not *per se* notifiable. It may be reported if found in a notifiable disease e.g., tuberculosis, or if the strain is sent to a PHLS reference laboratory. This surveillance system will not reflect the true prevalence of resistance in the community as defined in (b) above. It does often work to identify unusual resistance patterns (a) above. An example of this was the first reported recognition in the world of penicillinase-producing gonococci by Phillips in London in 1976.

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1.3.2 To achieve (B) above, systematic quantitative data must be collected. At present the process is random and depends on:

1. clinician requesting specimen from patient
2. laboratory identifying and testing isolate
3. laboratory methods used and definition of resistance
4. laboratory reporting centrally

1.3.3 To overcome these problems the PHLS and some other microbiology departments have organised the collection of strains from a range of peripheral laboratories which have been tested in a reference centre. This has produced good information, for example, on ampicillin-resistance in *Haemophilus influenzae* and multi-resistance in *Pseudomonas spp.*, and some information of the prevalence of penicillin-resistant pneumococci in the UK. These surveys all depend on variables 1) and 2). The strains collected will reflect the degree of bias in their collection. In general practice there is no accepted protocol for taking microbiological samples before starting antibacterials. Some GPs take urine samples from all patients presenting with symptoms of possible urinary tract infection, others from only those with recurrent attacks who fail treatment, and some take hardly any specimens. Clearly, recent therapy might influence both the nature of the pathogen (some inherently resistant strains are more commonly found in complicated, recurrent urinary infections) and the sensitivity of *Escherichia coli*, the commonest cause. To obtain a more accurate picture samples should be identifiably collected from each category (first episodes or recurrent infections). This will help decide the choice of antibacterial to be used empirically.

1.3.4 A common source of bias in sample collection is multiple sampling from the same patient and from groups of patients infected with the same strain in hospital due to cross-infection. Good IT systems are needed to identify duplicate sampling and to link clinical data with that in the laboratory. Most request cards accompanying samples contain far too little information. Ideally data should be only entered once in the laboratory to enable generation of a report to the clinician. These data should be linked by compatible computer systems to the hospital PAS. With the advent of computer links with general practice, it would be possible to combine information from these sources and compare it with prescribing rates (PACT data).

1.3.5 Most UK laboratories are not resourced to perform surveillance. Since epidemiological data is not directly linked to the care of individual patients there is no duty to provide it locally or centrally. The PHLS network of 48 laboratories and some NHS and University-run laboratories do collect bacterial strains of interest on a voluntary basis to send to central PHLS reference facilities or report to CDSC. Overall this has been a rather haphazard process and needs to be done systematically.

1.4 The clinical consequences of resistance

1.4.1 At its most basic level therapy is more likely to fail when using an antibacterial to which the invading bacteria are resistant in vitro than if they are sensitive. It is important to realise that because bacterial infections are usually acute, most antibacterial therapy is empirical since currently the routine isolation of the pathogen and determining its sensitivity to antibacterials often takes at least 48 hours. Therapy is based upon the likelihood of particular pathogens being present in the clinical circumstances and their likely sensitivity to antibacterials, both based upon previous experiences. Both are also influenced by where and when the presumptive infection is acquired, particularly whether it arose in hospital or the community, the former being characterised by having more resistant pathogens.

1.4.2 The choice of empirical therapy or prophylaxis is governed by experience, and an increased incidence of resistant strains is likely to result in changes in the policies governing both treatment and prophylaxis, often to newer ones.

1.4.3 A change in the routinely used antibacterial agents can have considerable monetary costs for the hospital and psychological costs for the patient. These include:

1.4.3.1 The use of an intravenous antibacterial instead of an oral one, with both higher acquisition and administration (non-antibacterial materials and staff time) costs, trauma to the patient, and perhaps in-patient rather than community treatment.

1.4.3.2 The use of an agent which is more toxic, with potential damage to the patient and litigation costs to the hospital. Some toxic antibacterials require blood-level monitoring which considerably increases their usage costs.

1.4.3.3 The change in prescribing may bring forward antibacterials previously reserved for difficult infections which increases their usage and may hasten the time when resistance increases to them as well.

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1.4.4 As mentioned above (1.1) antibacterial usage may not only select bacterial strains with acquired resistance but also inherently resistant species with a consequent increase in the proportion of infections caused by them. Good examples of this are enterococci (inherently resistant to cephalosporins) which become more prominent as hospital pathogens following the wide-spread use of cephalosporins, and the toxic entero-colitis caused by *Clostridium difficile* (inherently resistant to many penicillins and cephalosporins) which has become a major problem in recent years in hospitals and to a limited extent in the community. Such changes in the prevalence of bacterial pathogens can alter antibacterial prescribing in a similar manner to a rise in acquired resistance.

1.4.5 Other consequences of infection with resistant bacteria are increased lengths of stay (to treat infections via the intravenous route), less effective treatment (with increased morbidity and mortality), and an increased use of isolation of patients. All these cause greater treatment costs.

2. THE CURRENT ROLE OF MEDICAL MICROBIOLOGY IN THE UK IN DETECTING AND CONTROLLING RESISTANCE

2.1 The structure of microbiology and infection control services

The linch-pin of microbiology services in the UK is the medically qualified microbiologist practising in the NHS district general hospitals from where they serve both the hospital, or a group of them, and general practices in the area. England and Wales are unique in having the Public Health Laboratory Services (PHLS) which consists of some 48 peripheral laboratories based in DGHs, and a central facility in North London (HQ functions, reference laboratories, Communicable Diseases Surveillance Centre (CDSC)). In addition, substantial microbiology services are provided by academic microbiologists based in medical schools. There is also a small proportion of services in private laboratories. In all there are about 560 medical microbiologists of consultant standing (NHS Consultants, Professors, Readers, Senior Lecturers) (Table 1). The figures are not absolutely accurate because of the difficulty of collecting constantly changing data. There is a marked difference between the provision of medical microbiologists in the various centres of the UK, but whether this affects their effectiveness is not known.

All NHS hospitals have an Infection Control Team (ICT), almost always headed by an Infection Control Doctor (ICD) who is a Consultant Medical Microbiologist. There are about 240 ICDs in the UK. The other important members of the ICT are Infection Control Nurses (ICNs), who have specialist training for this role. There are about 250 ICNs in the UK, but some of these are part-time. This equates to about 1 ICN per 400 acute beds (the recommended figure in the USA is 1 per 250). ICTs not only function within hospitals but frequently give extensive advice to community activities (GPs and their teams, nursing homes, etc). The extent of this latter function depends on how much the local Health Authority can provide directly such specialist services. Within hospitals the role of the ICT is to set standards (by developing infection control policies), educate, audit the standards, and to provide everyday advice on implementation of infection control procedures. In the community infection control is the responsibility of the Consultant for Communicable Disease Control (CCDC). There are some 150 CCDCs or equivalent, of whom some 30 are Medical Microbiologists, the remainder being almost all trained in Public Health Medicine. Because infection passes constantly across both functional and physical boundaries there is a close liaison between infection control professionals from hospitals and the community.

Apart from the Medical Microbiologists and ICNs other professionals play an important part in diagnosing, treating and controlling infection. Science graduates with post-graduate training in diagnostic, reference and research laboratories (Clinical Scientists) play a valuable role, particularly in the larger centres. Some of the more senior Clinical Scientists have a Consultant equivalent status. Largely in the diagnostic laboratories, but also in others, Biomedical Scientists (formerly termed technicians) are the most numerous staff and the mainstay of everyday work. Some other clinical staff, such as Infectious Diseases physicians, have expertise in antimicrobial therapy. They are small in number, however, and tend to be only on the larger centres.

TABLE 1
Distribution of Consultant (and academic equivalent) Medical Microbiologists in the UK¹

	NHS Consultants	PHLS Consultants	Academics	Totals for regions	Approximate Population (millions)	Thousands population per Microbiologist
England	216	145	70	431	46	107
Wales	12	16	3	31	3	97
Scotland	55	Nil	34	89	5	56
Northern Ireland	10	Nil	3	13	1.5	115
Total	293	161	110	564	55.5	98

¹ Data on numbers from AMM survey supporting its Directory of Microbiologists (1997, in press).
NB: Data do not include PHLS Colindale (6 Consultants) and the Armed Forces (2 Consultants).

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2.2 The role of Medical Microbiologist

Within hospitals and academic departments the medical microbiologist fulfils five main functions, the parportion of each depending on the type of institution they serve:

- Directing the diagnostic laboratory
- Providing a clinical consultative service
- Leading the ICT in infection prevention and control
- Teaching (undergraduate and health professionals)
- Research

2.2.1 Directing the laboratory

Within a laboratory there may be more than one medical microbiologist, but one is designated as head of department and is managerially responsible. They lead a laboratory team (of mainly Biomedical Scientists, Laboratory Aides, and clinical staff) which should give a cost effective service to a high professional standard with excellent timeliness. Quick and accurate bacteriological diagnoses are important in helping to implement appropriate antimicrobial therapy. Most clinical laboratories in the UK have now been accredited by CPA (Clinical Pathology Accreditation), an organisation supported by the pathology professions, hospital management and the DoH.

2.2.2 Clinical consultation service

A clinical consultation service is provided round the clock, which can entail a heavy on-call commitment. The Consultant ensures that there is a rational use of the laboratory by clinicians and that reports on specimens are relevant and carry informative comments when appropriate. Important results (for example positive blood cultures, isolation of communicable pathogens, antibacterial blood levels) are often communicated out of hours by the on-call medical staff to clinicians. Units (such as ICU, haematology, transplantation) with complex patients prone to infection are often visited by the microbiologist on a regular basis, sometimes daily. Pro-active clinical advice may be given on important laboratory results, and reactive telephone advice is provided to both general practitoners and hospital clinicians. It is important to appreciate that typically some 40 per cent of the microbiology specimens processed by a DGH laboratory come from the community.

In relation to *antimicrobials* (and particularly antibacterials) the medical microbiologist has the following roles:

2.2.2.1 Trying to ensure that only clinically relevant bacterial isolates are tested for sensitivity.

2.2.2.2 Maintaining the quality of the antibacterial sensitivity tests. Sensitivity tests form part of the external QA materials provided by UK NEQAS, and all clinical laboratories participate in this.

2.2.2.3 Confining the reporting of results of tests of sensitivity to those that are clinically appropriate.

2.2.2.4 Disseminating information to users (both hospital doctors and GPs) on local (and when appropriate national) sensitivity patterns to guide them in the most effective use of antibacterials.

2.2.2.5 Playing a leading role in creating and maintaining an up-to-date antimicrobial formulary and also policies.

2.2.2.6 Monitoring compliance with 2.2.2.4.

2.2.2.7 Giving advice on antimicrobial therapy for individual patients. This includes providing an analytical service for blood assays of antimicrobial drugs and interpreting the results to clinicians.

2.2.3 Leading the infection control team

The ICD is normally the Consultant Medical Microbiologist and they provide leadership for the ICT. In this role they are usually accountable to the Chief Executive of an NHS Trust. The ICD is trained in all aspects of infection control, including epidemiology. A new diploma (DipHIC) has been established to provide a recognised qualification. Good infection control (which includes routine surveillance for infected patients, feedback of information to clinicians, and concerted action in containment measures) can reduce infection rates. Between five and 10 per cent of patients acquire an infection during their hospital stay and the figure should be kept as low as possible.

Minimising the incidence of infection is one way of reducing the use of antimicrobials. Infection and its treatment with anti-bacterials not only increases the risk to the patient and to the community from bacterial resistance but may also divert resources from other patients by increasing hospital stay and the number of investigations, as well as from the direct cost of antibacterials.

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2.2.4 Teaching

Microbiologists in medical schools may spend a considerable amount of time in undergraduate teaching and examining. Many in DGHs and medical schools are involved in their own departments in training junior medical staff. Within hospitals microbiologists are involved in the training and CME of junior doctors and consultants from other specialities in joint meetings and clinical audit. They also participate in training other staff, particularly in infection control theory and techniques.

2.2.5 Research

Hospital microbiologists have been and still are leaders in antimicrobial research, and much of the published research has come from them. However, some Consultants are currently able to do research because of time and funding constraints. Clearly those in academic centres are expected to, and often undertake research of a highly scientific nature. Many DGH Consultants also do research, sometimes directed at the applied side of microbiology, such as antibacterial usage, laboratory diagnosis, clinical trials, and infection control.

2.3 Pressures on microbiology and infection control services

The number of medical microbiologists has remained approximately constant or even fallen over the past few years while the workload of their laboratories has increased substantially. Using data gathered from 49 hospital departments of microbiology (The Clinical Benchmarking Co, 1997) serious concerns were expressed about the inadequacy of the numbers of microbiologists and the way this impinged unfavourably on infection control activities and thus the prevention of hospital acquired infection. The data also showed that the number of population served had increased per WTE Consultant microbiologist. This is at a time when there are more patients in hospitals who are prone to infection because the practice of medicine has changed, there being more invasive diagnostic and therapeutic interventions and more patients with reduced defences to infection (for example: immunosuppression as a result of therapy, patients on ICU as a result of complex surgery). The efficiency of hospitals has increased by raising the throughput of patients. The resulting reduction in length of stay has had hugely adverse implications for infection control.

2.3.1 Because of reductions in bed numbers and the high bed occupancy there are few or no empty beds in appropriate wards and patients are moved from one ward to another during their stay, sometimes more than twice. Any infection they are carrying is therefore spread to a number of wards.

2.3.2 It is difficult to close a ward or cohort patients with infection on a ward, both manoeuvres used to control an outbreak of infection, because this would result in a major disruption of services with, for example, many cancelled operations or acutely ill patients being denied admission.

2.3.3 The rapid turnover of patients puts enormous pressure on ward staff (both nurses and doctors) who tend to minimise or omit important infection control procedures such as hand washing. The pressure also gives rise to high sickness rates necessitating the employment of bank and agency staff; this is not only expensive but such staff are sometimes poorly versed in infection control technique and are often unfamiliar with a particular hospital's procedures.

2.3.4 There is no time for adequate environmental cleaning between patients, even when they have been infected. This is in addition to the poor quality of general cleaning found in many hospitals, a contribution to which is cost improvements in domestic services.

2.3.5 All the above are compounded by the unsatisfactory quality of much of the hospital building stock. Few hospitals have enough single rooms for the isolation of infected patients. The poor provision of readily accessible hand basins discourages staff from following good hygiene.

3. FUTURE ACTIONS TO COMBAT RESISTANCE

3.1 Usage of antibacterials

If it is accepted that antibacterial usage has been responsible for increasing resistance and is likely to do so in the future it is legitimate to ask what might be done to restrict usage. Human usage accounts for some 50 per cent of the total production of antibacterials. In the developed world most antibacterial usage is by physician prescription. Some prescription usage is fully justified; some is perhaps not founded on the best evidence-based practice but may be justified by medical, cultural or psychological reason. A small proportion is perhaps completely without justification. Since there is doubtless a continuous gradient of justifiability these distinctions are somewhat artificial but serve to illustrate the argument. In discussing control of prescribing it is assumed that the first category would be unaffected. Education in and audit of antibacterial prescribing may reduce the second and eliminate the third but it is "guesstimated" that at very best usage may be reduced by 20 per cent and realistically by perhaps as little as 5 per cent. The effort to sustain improvement will have to be continuous, with huge resource implications, if any beneficial effect is to be maintained. It is thus appropriate to ask the

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question whether this reduction to justifiable usage only will have a significant impact on the progression of resistance let alone reverse it, and we believe it is unlikely to do so even if the UK population were exposed only to resistance genes from itself. As it is, unless something is done on a larger scale resistance genes will continue to be generated, maintained and transferred to human from animals in the food-chain and from humans in countries where similar controls are not exerted. This point is made not to excuse the medical profession's seeming unwillingness until now to place tighter controls on antibacterial usage but to put such controls into perspective and to make a judgment on their likely effectiveness.

3.2 *Actions to improve the usage of antibacterials*

3.2.1 *Where are antibacterials prescribed?*

In the UK both topical and systemic antibacterials are prescription-only medicines and thus require a doctor to prescribe them. Dentists can also prescribe some antibacterials from a dental formulary. The large majority of prescriptions for oral antibacterials are written in general practice. In 1992–94 some 270 million defined daily doses of antimicrobials (almost entirely antibacterials) were prescribed annually by GPs in England, enough to treat every member of the population of England for 5 days a year (Prescription Pricing Authority (PPA) Annual Report, 1995–96). The use of antibacterials by GPs increased by an average of about 5 per cent a year from 1989 to 1991 (Davey *et al.*, 1996) without seemingly being justified by a similar increase in morbidity from infection, although the upward trend seemed to level off in 1993 (PPA, 1995–96). There was also evidence that the increased prescribing was for newer antibacterials at the expense of older ones.

Parenteral (intramuscular and intravenous) antibacterials are currently almost entirely confined to hospital use. National data are not readily available but from sales figures (kindly provided to the AMM by Merck Sharp and Dohme, Business Planning Department) we estimate that there are about 1–2 million treatment days a year given by the parenteral route to patients in hospitals in England (*cf* figures for GP prescribing given above). As a check on this estimate we calculated hospital use of antibacterials by another approach. There are about 85,000 acute hospital beds in the UK which yield some 30 million bed-days. Studies have shown that about 30 per cent of patients receive an antibacterial at sometime during their stay making a maximum of 10 million possible days of antibacterial therapy. However, many patients only receive a short course for prophylaxis and thus the true figure for antibacterial treatment days is like to be much lower, probably less than 5 million. While this does not agree closely with the estimate arrived at from the sales figures, it serves to confirm how much smaller exposure of patients to antibacterial therapy is in hospitals than general practice. The use of oral antibacterials in hospitals is relatively low. Thus the total usage of antibacterials by prescription in hospitals is considerably less than in general practice. It should also be remembered that oral therapy necessarily exposes concomitantly to an antibacterial the intestinal bacterial flora (including that of the mouth), which contains by far the greatest concentration of both numbers and variety of bacterial species compared with other body sites (e.g., faeces contain 1,000,000,000 bacteria per gram). Conversely, the adverse effect of at least some intravenous antibacterial therapy on the intestinal flora is negligible. Thus any measures to improve and control antibacterial prescribing must be effective in both general practice and hospitals.

A considerable proportion of the use in hospitals is for prophylaxis against infection during surgery, perhaps 20–30 per cent of the total patient days of therapy. Although this does reduce post-surgical infection, audits of this use have shown that courses given are often longer than necessary.

Oral antibacterials are presently not available to the public from pharmacies without prescription. The Association is aware of the current interest in the over-the-counter availability of antibacterials and the impending report on it from a Working Party (of which Professor Reeves is one of its two joint Chairmen) of the British Society for Antimicrobial Chemotherapy, and will be making comments on the report when it is available.

3.2.2.1 *Antibacterial formularies and use policies*

Most hospitals and some general practices have at least a formulary of antibacterials (that is a list of antibacterials available and sometimes indications as to what seniority of medical staff may prescribe individual agents). Some hospitals have antibacterial policies. These are documents that give guidance on the use of antibacterials in various frequently encountered clinical circumstances. Both formularies and policies are usually created by multidisciplinary co-operation (clinicians, microbiologists, pharmacists, etc.), compliance being thought to be optimised by ownership. All hospitals and general practices should have policies for antibacterial prescription.

There is evidence that nationally concerted action can influence resistance. An increase in resistance of streptococci (an important bacterial cause of sore throat) to erythromycin in Finland was countered by a policy restricting the use of macrolides (a type of antibacterial of which erythromycin is one) (Seppala *et al.*, 1997). Consumption was reduced by nearly a half by 1992 and resistance was nearly halved by 1996. It should be pointed out, however, that erythromycin resistance is unusual in that it seems to be readily reversed to sensitivity when the selection pressure is decreased.

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3.2.2.2 *Monitoring the effectiveness of formularies and policies*

The effectiveness of having policies is difficult to determine and is best done by *audit*. This is however very labour intensive for the professionals concerned unless there is computerisation of prescribing and clinical details since records must be searched by hand. Very few (or perhaps no) hospitals in the UK have the IT which would facilitate such audits. Information on prescribing by individual doctors is often better in general practices, many of which have computerised prescribing systems which also record a simple diagnosis. Justification for the prescription would still have to be hand searched in many instances. Recent evidence from the USA (White et al, 1997) shows that it is possible by considerable effort (prior approval from an infection specialist for the use of an antibacterial from a restricted list) to influence prescribing without adversely affecting clinical outcomes and with improvements in the sensitivities of bacteria.

3.2.3 *Medical education*

If the quality of antibacterial prescribing is to improve then there needs to be an increased educational effort at all levels from undergraduate upwards. In the main oral antibacterials are not toxic drugs and have a wide therapeutic margin and rarely cause serious adverse effects in individual patients, which can induce a casual attitude to prescribing them ("Oh well, we'll give it just in case"). While this might occasionally benefit individual patients the exposure of the body flora to antibacterials tends to select out resistant strains with consequential potential disadvantage to the community. Thus the antibacterials are victims of their own success, most doctors feel confident that they prescribe them well, and prescription is often delegated to junior medical staff in hospitals. The undergraduate curriculum is crowded and now constrained by the requirements of the GMC; priority should be given by the medical profession, universities and the GMC to ensuring that a definitive slot on antibacterial use is in all curricula and that this includes not only technicalities of antibacterials but puts their use into sociological and world contexts. It should be remembered that antimicrobials are the only class of drugs the prescription of which can have adverse consequences outside individual recipients and this unique position mandates their special place in therapeutic teaching.

In hospitals continuing education is best accomplished by multidisciplinary audit of antibacterial prescribing. This is, however, labour intensive for microbiologists' time in the absence of suitable IT, as explained above.

General Practitioners receive detailed information, if they wish it, on their prescribing from the PPA (PACT data). Further information may be available on their practice computer. As in hospitals, multidisciplinary audit may well be the best educational tool but access to antibacterial expertise is limited. Microbiologists do not have enough time to spend it continuously collaborating in audits with the GPs to whom they relate.

3.2.4 *Improving the collection and quality of data on the epidemiology of resistance* This is fully described above at 1.3.2-5.

3.2.5 *Guidance from the microbiology laboratory*

3.2.5.1 *Restrictive reporting of antibacterials*

Many, or indeed most, laboratories in the UK practice restrictive reporting of antibacterial sensitivities on pathogens isolated. That is, they only test a restricted range of antibacterials and even they do not report all the sensitivities tested. Reporting is tailored to what is felt to be appropriate for the individual patient and the wider context and is often also made to be concordant with the hospital's formulary and antibacterial policies.

Pressure, usually resisted, can be put on laboratories to report additional and perhaps unsuitable antibacterials. This is done by pharmaceutical companies interested in raising the profile for an antibacterial, and sometime by laboratory users (i.e., doctors) who may have unconventional views on what is appropriate antibacterial therapy. Threats of taking their pathology requests elsewhere are occasionally made by the latter if fund-holders, something which has taken on a real meaning in the current quasi-market of the NHS.

3.2.5.2 *Guidance on the significance of isolates*

Microbiology laboratories do not report all bacterial isolates from many of the specimens they receive. This is because a judgment is made as to which are likely to be acting pathogenically, or which may be part of the normal body flora or contaminants. This is important for antibacterial use since it avoids prescriptions for "treating" bacterial isolates which are not causing infection. Further guidance is often provided by written comments on reports, the telephone, or visits to wards. This may take the form of not only discussing the significance of isolates but also appropriate antibacterial therapy.

3.2.6 *Reducing the incidence of infection*

Antibacterial usage arises directly from the need to treat or prevent infection. It follows therefore that a reduction of infection will result in using less antibacterials.

3.2.6.1 In hospitals efforts must be increased to prevent patients acquiring infection, especially with bacteria resistant to many antibacterials since this may increase the use of new and expensive antibacterials. More

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research should be made available not only to sustain or improve the professional input to infection control (both at the level of advice and application) but to raise environmental standards, such as intensified cleaning schedules (the current state of cleanliness of many clinical areas being disgracefully poor) and the provision of more single room accommodation to isolate patients.

3.2.6.2 In the community a reduced incidence of bacterial infection would come about largely through general improvements in health, especially with regard to respiratory infection, and by public education on infection avoidance. Examples of the latter are improved awareness of how to avoid food-poisoning by maintenance of kitchen hygiene, and avoiding urinary infection associated with sexual intercourse by following simple measures. There is evidence that despite increased public concern about infection from food, safe handling of food in the home is not widely practised (Hyde, 1997).

3.2.6.3 Vaccines have played a major role in reducing the incidence of many viral and some bacterial diseases. Of the bacterial infection prevented on a population basis (tetanus, diphtheria, tuberculosis, pertussis) two are medicated by the production of a toxin against which the vaccine is directed and are thus easily affected targets. Other bacterial infections, and in the community respiratory, urinary and soft-tissue infection are the commonest by far, are caused by a wide variety of bacterial pathogens. Furthermore, the incidence of these is not high, they are generally not readily communicable, and some are unpleasant but not life-threatening. It is therefore difficult to see how a population-wide vaccination programme against such bacterial infections could be implemented (even assuming effective vaccines are researched and manufactured, since they do not presently exist) or be cost effective.

Hospital-acquired infections are caused by a wide variety of pathogens. Furthermore, many patients have concomitant conditions which might well reduce their immunological response to vaccines. It would be impracticable to attempt to vaccinate prophylactically patients against the huge variety of infections they may encounter, and because of the delay in response to a vaccine it would not be effective in an acute infection when it occurred.

Although this paints a gloomy scenario the importance of vaccines in controlling infection must not be underestimated. Research into vaccines should be encouraged since, if we fail to control resistance and infections become untreatable with antibacterials, vaccines may become a vital modality in preventing infection.

3.2.7 *Non-human use of antibacterials*

Only about half the world production of antibacterials is used in human medicine. The remainder is used largely in veterinary medicine and animal husbandry (mainly the latter) for disease prevention and growth promotion (The World Health Report 1996). Developed countries, such as the USA, follow this pattern of usage (Institute of Medicine 1989). We realise that this issue is not the focus of the Sub-Committee's enquiry but we believe the influence of this use is so large in generating and maintaining resistance genes in the animal population which inevitably reach humans via the food-chain, that not to mention it would be remiss. There are clear examples of zoonotic pathogens resistant to antibacterials infecting humans, such as salmonellosis. For every symptomatic human case there will be many more where exposure to the pathogen, and hence resistance genes, occurs. Action to reduce resistance in the future should be multi-factoral and the use of antibacterials in animals must be considered as one facet. A important step forward will be to separate regulation of food safety from responsibility for its efficient production in the creation of the Food Standards Agency.

3.2.8 *Educating the public*

3.2.8.1 *Use of antibacterials*

Some pressure for prescribing arises from public expectation. Responsible use of antibacterials is in everyone's interest and is thus everyone's business. Government (presumably through the DoH, but perhaps also via secondary education), the health professions, and the news media should all take seriously education of the public in the risks of the overuse of antibacterials and why it should have a responsible attitude towards them.

The Association has made a serious effort to inform the general public and other interested people (e.g., Environmental Health Officers) on various matters about infection by producing and making available the "Facts About . . ." leaflets (A file of the leaflets will be given to the Sub-Committee.) The Association is considering producing one on public health aspects of antibacterial resistance. The Association also produces a journal largely for its own membership but which could be adapted in part to a wider educative role. It also has a Web site which could be used for the same purpose.

The news media should improve their handling of matters vital to public welfare by avoiding sensationalising their reporting and using teams of informed professionals at all stages in the production of material for broadcasting. In other words, programmes and reports should be more attuned to educating and informing rather than raising ratings and sales. Because we realise that commercial considerations constrain the media we suggest that there should be partnership with government in some public information programmes and reports.

3.2.8.2 *Avoiding infection*

The same agencies should be involved in informing the public how to avoid infection (see 3.2.8.1 above).

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3.2.9 Improving diagnosis of bacterial infection

Prescription of an antibacterial can be better targeted by knowing the actual pathogen and its sensitivity or avoided altogether by knowing no bacterial infection is present. As explained above (1.4.1) because of the slowness of most laboratory diagnoses most antibacterial therapy of infection is empirical. Research into more rapid diagnostic methods is essential as is their development into routine use. Funders of research should note this priority. Government should consider partnerships with industry so that commercially unprofitable lines can be followed. Rapid methods are likely to be more costly in application than those currently employed so the providers of laboratory services will have to give high priority to funding them. A recent review concluded, however, that traditional methods are very unlikely to be replaced completely in the foreseeable future (Altwegg and Kayser, 1997).

3.2.10 Improving knowledge about resistance

Although much research has been published into the biochemical and genetic basis of resistance there are still considerable gaps in our knowledge. The epidemiology of resistance is still poorly understood because of the haphazard way data are collected on local, national and international scales (see 1.3). There is a need for a more systematic approach to data collection involving looking at defined patient populations, collecting denominator data, and standardised laboratory methods and definitions of resistance, all of which will require increased resources from government. In determining the influence of antibacterials on resistance existing data on their usage (such as that held by the PPA) should be made freely available to scientific researchers. Because resistance pathogens spread internationally governments in the developed world should consider what help could be given to developing countries to assist in examining their problem of antibacterial resistance and how it might be controlled.

3.2.11 Role of government

Possible governmental actions have already been outlined and will not be repeated here. Action on resistance now is a difficult political matter since it requires diverting resources from other priorities in the short term and perhaps taking an unpopular stance on some things for what is an uncertain gain (both in terms of timing and quantity) in the future. For example, reducing antibacterial use in animal husbandry would mean the public would have to pay more for the same amount of meat and the profitability of meat production might also be adversely affected. More resources put into hospital cleaning might result in longer waiting times for treatment. Nevertheless, we believe strongly that resistance to antibacterials is presently a problem of sufficient magnitude in causing suffering to patients and raising treatment costs and is likely to worsen in the future and that high priority should be given to ensuring that corrective action is taken.

3.2.12 Role of industry

The pharmaceutical industry has a role to play in improving the way antibacterials are used. While the ultimate responsibility for human use lays almost entirely with the medical profession, the effect of promotional activities cannot be ignored since they must have a favourable outcome for the companies doing them or they would cease. Not only has the total number of prescriptions of antibacterials per capita increased without a seemingly good reason, but industry succeeds in persuading doctors to substitute high priced scripts for cheaper ones, with an adverse effect on health service resources.

3.2.13 Action on a international scale

Easy and cheap world-wide travel facilitates the spread of resistant bacteria. Thus actions (or lack of them) to control resistance in other countries are of direct relevance to the UK. A dramatic example of the spread of resistance was the introduction and explosive spread of penicillin-resistant pneumococci in Iceland. Subsequent studies of the genetics of the strain showed that it almost certainly came from Spain, where it was common and the usage of oral antibacterials is high. Thus the government should seek to raise the profile of antibacterial resistance in Europe. A first step would be to create a common pool of information on the epidemiology of resistance using data collected by systematic surveillance (as discussed at 1.3) and on the usage of antibacterials both in hospitals and the community. Usage should be linked to diagnosis i.e., the rationale for it. The current lack of publicly available data in the UK on hospital usage is deplorable. Such collection of data that is done is by commercial companies which sell it on to marketing departments, and as such it is not freely available. A serious attempt should be made to control resistance within Europe since it would be difficult to target developing countries before its own house were in order. Some countries, particularly those on the Mediterranean littoral and in eastern Europe, have poor records both in resistance and usage.

Ultimately, however, government should collaborate more intensively with global agencies, and may consider initiatives of its own, to help countries outside Europe study and control antibacterial resistance. The problems of controlling antibacterial usage in developing countries are almost insuperable, and will depend on improvements in health services and improvements in the health of their populations. Of interest is the recent report that that resistance had reached such a level in Uganda that doctors were calling for a temporary ban on the availability of antibiotics from chemists (Kigotho, 1997).

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3.3 Providing new antibacterials

The past 10 years or so have seen a marked fall in the number of new antibacterials with novel modes of action (as opposed to those with actions resembling those already available) reaching clinical practice. The main reasons for this are, firstly, that it is difficult to find or create, as their numbers increase, truly novel agents which are patentable; there may well be a finite number of targets in bacteria susceptible to antibacterials and thus it becomes incrementally more difficult to find novel agents. The second reason follows from the first in that it is commercially unattractive to invest in research having little chance of producing a return. As a result, the number of companies investing in antibacterial research declined even before the recent trend towards company mergers occurred. Governments in the developed world must consider how they can interact with industry so as to encourage research and development of new antibacterial entities which will hopefully have activity against strains of bacteria otherwise resistant to antibacterials. The development of antibacterials with narrow antibacterial spectra should be encouraged so as to combat specific problems of resistance (e.g. MRSA and VRE) and to facilitate better directed prescribing. Because such antibacterials have limited indications (so called "orphan drugs") and thus commercially unattractive, Government could help in their development by altering the regulatory environment. Examples might be fast-tracking to regulatory approval and increasing patent life.

As important as the introduction of new antibacterials is, it will only provide short or medium-term respite unless innovation continues. Experience has shown that bacteria eventually develop resistance to new agents, although this may take a long time, as in the case of vancomycin-resistant MRSA which were only reported recently.

(Three examples of infections resistant to antibacterials are given in Appendix 1 to illustrate what needs to be done in specific instances)

3.4 Prioritising the actions to control resistance (Table 2)

Many of the recommendations made above for actions to combat resistance are based on opinion rather than evidence. Not only is it unclear as to which would be the most effective but also the extent to which each might be effective and how much it could cost. Nevertheless, we feel that an attempt should be made at prioritising what is a long list, and the following are in our priority order.

3.4.1 Improving human usage (see 3.2.2.1 and 2,3.2.3)

Although for the reason stated at 3.1 this might well have a limited effect, the medical profession must put its own house in order before it can expect others to do so. Furthermore, unless effort is made on all fronts, any failure to control resistance will by the nature of things be blamed on actions not being taken.

3.4.1.1 All doctors should prescribe antibacterials from peer-reviewed and agreed formularies and according to policies for usage. The DoH should strongly encourage this.

3.4.1.2 Compliance with 3.4.1.1 should be audited. This will require in the short-term investment in skilled manpower, such as pharmacists and other experts in antibacterial use. In the long term, investment in IT (electronic prescribing and clinical records, with linkage between them) will be necessary. The difficulties of auditing the actions of GPs will be considerable. The costs to the NHS of implementing 3.4.1.1 and 2 will be high.

3.4.1.3 Changes to the undergraduate curriculum will have low financial implications (although painful for the organisers of it!) and should be implemented immediately. Post-graduate education is best linked to the creation of guidelines and policies, and to audit (as above).

TABLE 2
Prioritising the actions to control resistance (paragraph 3.4)

Action (paragraph in text)	When to implement	Successful impact:			Direct costs to:		
		Likelihood	When	NHS	Government	Commercial interests	Public
<i>Improving human usage (3.4.1)</i>							
Formularies and policies (3.4.1.1)	Now	Some effect, but not major	5–10 years	Low	Nil	Loss of sales	Nil
Audit of usage and postgraduate education (3.4.1.2)	As soon as IT permits	"	"	Considerable if IT-driven	Nil	"	Nil
Undergraduate education (3.4.1.3)	Now	"	"	Nil	Nil	"	Nil

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Action (paragraph in text)	When to implement	Successful impact:			Direct costs to:		
		Likelihood	When	NHS	Government	Commercial interests	Public
<i>Collecting good data on epidemiology of resistance</i> (3.4.2)	Now	No direct effect, but informs other actions		Moderate (mainly lab. and IT)	Nil	"	Nil
<i>Preventing infection</i> (3.4.3)							
Hospitals (3.4.3.1)	Now	Considerable	Within 5 years	High	Political costs may be high	Nil	Some increase in W/Ls
Community (3.4.3.2)	Now	Small or moderate	Within 5 years	Low	Low	Some to nursing homes	Nil
<i>Restraints on the pharmaceutical industry</i> (3.4.5)	Now	Moderate	Within 5 years	Nil	Nil	Moderate	Nil
<i>Non-human use of antibacterials</i> (3.4.6)	Within 5 years	Strong effect on some resistances	5–10 years	Nil	Highly political	High	Moderate
<i>International co-operation</i> (3.4.7)							
European (3.4.7.1)	Now	Considerable if successful	>10 years	Nil	Moderate	None (but loss of sales if usage restricted)	Nil
Wider (3.4.7.2)	Later (>5 years?)	Intangible (actions uncertain at present)	>20 years	Nil	Unknown (but could be very large if desired)	"	Nil
<i>Improving diagnosis of infection</i> (3.4.8)	Now	Strong effect if successful	>10 years	Moderate to implement	Nil	Nil (may benefit)	Nil
<i>Providing new antibacterials</i> (3.4.9)	Now	Considerable if successful	>10 years	Moderate if new agents used	Nil	Nil (may benefit)	Some, if pay of new drugs

3.4.2 *Collecting good data on the epidemiology of resistance* (see 1.3)

Systematic collection of epidemiological data on resistance should be initiated immediately so that baseline information is obtained before actions to reduce resistance are implemented, and then continued in the long-term. In this way the effectiveness of the sum of action can be evaluated. The costs to the NHS are likely to be modest compared with many other actions.

3.4.3 *Preventing infection* (see 3.2.6)

3.4.3.1 Preventing infection from recurring in hospital patients will require considerably greater resources for hospitals for:

- better domestic standards
- more front-line staff
- more expert staff to train and audit other staff
- reducing pressure on beds

All these would have huge direct and opportunity costs to the NHS. Political costs may be high if the total NHS resource is not increased.

3.4.3.2 In the community some dividends would be returned by public education on infection avoidance. Compared with the improvements needed in hospitals, this would be relatively inexpensive.

3.4.4 *Reducing public expectations* (see 3.2.8)

Much of the pressure on GPs to prescribe antibacterials comes from their patients. More public education is needed on the social consequences of overuse of antibacterials. This should be started soon and would be relatively inexpensive.

3.4.5 *Restraints on the pharmaceutical industry* (see 3.2.12)

The success of the pharmaceutical industry in promoting new antibacterials is borne out by prescribing data. Some of this use has no clinical justification, and stricter controls should be put on the industry so that over-zealous promotion is restrained. We recognise the value of a free-market in sustaining the success of pharmaceutical companies which in turn finances research, but consideration should be given to more emphasis

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[Continued

on clinical need uniquely when granting licences for new antibacterial agents in view of their possible adverse effects on society. The public cost of this action would be low and it should be implemented soon.

3.4.6 *Non-human use of antibacterials* (see 3.2.7)

This is clearly a highly political action in that while the direct costs to the NHS will be negligible the financial implications for producers and consumers will be large. This action is only likely to be achieved in the medium term, but the issue cannot be avoided.

3.4.7 *International co-operation* (see 3.2.13)

3.4.7.1 Within Europe a common pool of data on the epidemiology of resistance and antibacterial usage should be created by means of systematic surveillance. Such data should be widely available to interested parties.

3.4.7.2 A later step should be to offer help to non-European countries in the control of resistance.

3.4.8 *Improving the diagnosis of infection* (see 3.2.9)

Better directed antibacterial therapy would follow more rapid aetiological diagnosis. Research into improved diagnostic methods would be of necessity somewhat speculative, and encouragement should be given to industry to follow this line. Since the introduction of new methods would probably raise direct diagnostic costs, more NHS resources should be made available or the products will fail financially. The research costs will be relatively low in government terms but implementation may be expensive for the NHS. Enhanced research should start soon.

3.4.9 *Providing new antibacterials* (see 3.3)

Encouragement should be given to the pharmaceutical industry to develop new antibacterials. The regulatory environment could be changed to help the viability of new antibacterials with limited indications.

ACKNOWLEDGEMENTS

The Association is grateful to the many members of its Executive Committee who contributed to the construction of this evidence, particularly to Dr Wright who compiled the glossary at short notice. Dr Deirdre Lewis (CCDC, Wiltshire HA) kindly put the President's version of 1.1 and 1.2 into readable English. Thanks are due to the Clinical Benchmarking Company for permission to refer to their report, and to Merck Sharp & Dohme (Business Planning Department) for data on the hospital use of antibacterials.

BIBLIOGRAPHY

- Altwegg M, Kayser F H (1997). Will cultures survive? The role of molecular tests in diagnostic bacteriology. *Infection* 25 265–8.
- Davey P G, Bax R B, Newey J *et al* (1996). Growth in the use of antibiotics in the community in England and Scotland in 1980–93. *British Medical Journal* 312 613.
- Hyde B (1997) Consumers concerned about food contamination but don't use safe practices at home. *ASM News* 63 352.
- Institute of Medicine* (1989). Human health risks with the subtherapeutic use of penicillin or tetracycline in animal feed. Washington, D.C.: National Academy Press: 65–7.
- Kigotho A W (1997) Ugandan doctors request an antibiotic moratorium. *Lancet* 350 1014.
- Pathology Feedback Report (1997) Microbiology. Clinical Benchmarking Company Ltd (*Confidential report*).
- Prescription Pricing Authority, Annual Report 1995–1996. Insert on *Antibiotics*.
- Seppala H, Klaukka T, Vuopio-Vakila J *et al* (1997). The effects of changes in the consumption of macrolide antibiotics on erythromycin resistance in Group A streptococci in Finland. *New England Journal of Medicine* 337 441–446.
- The World Health Report 1996* World Health Organisation, 1996 (ISBN 92 4 1561823) p.19.
- White A C, Atmar R L, Cate T R, Stager C E, Greenberg S B (1997). Effects of requiring prior authorisation for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. *Clinical Infectious Diseases* 25 230–9.

FIGURE 1

Supervised single dose therapy is used in the treatment of gonorrhoea because of problems in compliance with longer courses. This type of therapy is clearly more likely to fail than a course of multiple doses. As strains of gonococci became more resistant with the passing of time the dose had to be increased. Eventually some strains were so resistant that therapy with penicillin was abandoned.

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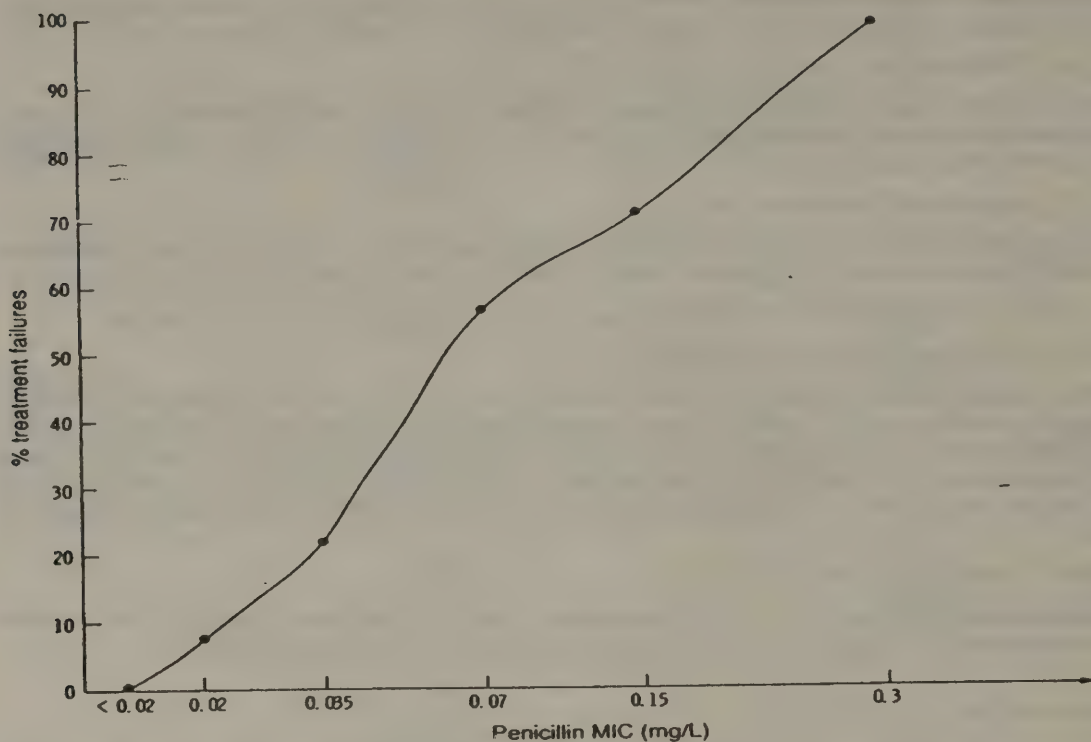


Fig. 24.4 Correlation between minimum inhibitory concentration (MIC) of penicillin for *N. gonorrhoea* and failure of treatment with a single dose of 300,000 units of penicillin in the treatment of acute gonorrhoea in men. (Data from Curtis F R, Wilkinson A E 1958 *British Journal of Venereal Diseases* 34: 70-82.)

APPENDIX 1A

Methicillin—resistant *Staphylococcus aureus* (MRSA)

After a number of years of relative freedom from MRSA in the 1970s, the 1980s and 90s have witnessed a dramatic rise in the number of patients in British hospitals colonised or infected with it. A similar change has occurred in other countries. The increase has probably resulted from the emergence of epidemic strains of MRSA (EMRSA) with a high degree of communicability. Factors which may have furthered this epidemic are high levels of antibiotic usage, the frequent movement of patients between wards ("hot bedding") because of the shortage of beds, and poor standards of cleaning (*S. aureus* can survive in dust). Infection Control Teams have put huge efforts into attempting to control EMRSA in many hospitals, seemingly without being able to stem the increasing frequency of the colonisation or infection of patients, at least partly because of the difficulties in influencing the environmental factors mentioned above. Apart from the manpower, these effects have cost huge sums in extra screening tests for EMRSA, in treating carriers, in colonised staff put off work, and by disruption to the running of hospitals for ward closures and cohorting colonised patients. The increase of EMRSA has resulted in infections which can only be treated with antibacterials (glycopeptides, mostly vancomycin) which are given intravenously, expensive, and require drug-level monitoring. *An example of this is given in the Table attached to this Appendix.* In units where EMRSA is endemic empirical therapy and prophylaxis is with these antibacterials instead of cheaper ones. The increased use of glycopeptides has created worries that MRSA would acquire resistance to them. For some years this gloomy prophesy remained unfulfilled but 1997 has seen reports of a handful of isolations of vancomycin-resistant MRSA in Japan and the USA. It is only a matter of time before this occurs in Britain and patients are infected with what are currently virtually untreatable bacteria.

LESSONS

- We managed to contain MRSA, despite high antibacterial usage and poor hospital environmental practices, until highly communicable strains emerged.
- The costs of attempting to contain the epidemic and of failing to do so have been vast.

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[Continued

- More emphasis must be placed upon having environmental conditions in hospital (reduced antibacterial usage, less patient movement, more isolation facilities, better environmental cleaning) if we are to contain these highly communicable and dangerous bacteria.
- Resources must be put into developing antibacterials active against vancomycin-resistant MRSA.

TABLE FOR APPENDIX 1A

Increase in MRSA in a 1,000 bed DGH, the rise in serious infections with MRSA, and the need for a greater use of vancomycin

Year	Total patients newly positive with MRSA ¹	Blood cultures positive for MRSA ²	Vancomycin blood assays in patients with MRSA ³
1994	22	0	1
1995	40	3	5
1996 ⁴	327	15	26
1997 (to 14/9)	389	27	43
(1997 projected FYE)	(549)	(38)	(61)

¹ Patients colonised or infected.² Positive blood cultures are taken as an index of serious infection.³ Vancomycin treatment is monitored by assays of its levels in blood. The number of them is taken as an index of vancomycin usage in patients infected with MRSA in the absence of good data on prescribing.⁴ During 1996 some 20,000 swabs (at a cost of about £30,000) were taken from patients and staff to screen for MRSA, as part of action taken to define and control the rise in MRSA colonisation and infection.

Source: (Data from Southmead Hospital, Bristol).

Comments on Table:

Data were taken from Southmead Hospital, Bristol, not for parochial reasons but because they were easily accessible. The increase shown in MRSA will be repeated in most hospitals in the UK, although a high prevalence has existed for many more years in some hospitals, especially in London. The increased treatment costs for patients with MRSA are the acquisition cost of vancomycin (or the alternative glycopeptide antibacterial teicoplanin), the cost of giving it intravenously, and the drug monitoring costs (about £15 per assay).

APPENDIX 1B

Clostridium Difficile Infection

C. difficile inhabits the bowel of some people without causing any symptoms or harm. It is naturally resistant to a number of antibacterials, and when one of these is given to a patient for the treatment of an infection bacteria in the bowel (other than *C. difficile*) can be reduced in numbers as an unintentional side-effect. This can allow *C. difficile* to increase greatly in number by filling the empty ecological niche. If the strain is one producing toxin the lining of the bowel can be severely damaged resulting in an entero-colitis. At worst the patient may die of this, particularly if they are weakened by other disease, but in any event the condition is distressing for them, delays their recovery and increases their length of stay, incurs cost for diagnosis and treatment, and may cause the patient to be isolated. Outbreaks of this infection have caused the closure of wards, and some nursing homes refuse to accept patients to be discharged to them without evidence they are not infected. This condition was originally thought to be one of hospitalised patients, but it is now apparent that use of antibacterials in the community is causing cases there. *C. difficile* can exist in the environment in a spore form resistant to drying, light and disinfectants (unlike many bacteria which are killed by these physical insults) and can be found contaminating hospital equipment furnishing, and structures when this is not adequately cleaned from which it can spread to other patients.

LESSONS

- A bacterium with natural (inherent) resistance can behave like one with acquired resistance when exposed to ecological pressure from antibacterials.
- Poor hospital cleaning and environmental hygiene allow the spread of this resistant bacterium to other patients.
- This complication of antibacterial therapy needs to be considered in the risk-benefit equation when contemplating antibacterial therapy in hospital and the community.

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APPENDIX 1C

Multiply drug-resistant *M. tuberculosis* (MDRTB)

Recent outbreaks of MDRTB infection in London and the USA have highlighted the additional dangers posed by antibacterial resistance in tuberculosis to hospital patients and staff, and potentially the public at large. At least one outbreak derived from a patient from abroad where control of therapy is less well done and where laboratory tests for resistance are often not done. Treatment of the infections is difficult because the second-line antibacterials used are less effective, and are more toxic and difficult to take. Diagnosis and the institution of appropriate therapy is hampered by the slowness of tests (because *M. tuberculosis* grows only slowly in vitro) for detection, identification and sensitivities. Infection control was difficult in London because of a lack of isolation facilities of sufficient standard reliably to prevent spread to staff and other patients.

LESSONS:

- Developed countries are vulnerable to infections from abroad, and combating resistance cannot be a parochial activity.
- Investment in developing new drugs is vital.
- More research is needed into improving (particularly with regard to speed) tests for the detection and sensitivity to antibacterials of bacteria.
- Improvements in isolation facilities are urgently needed.

GLOSSARY AND ABBREVIATIONS

Aetiology: the cause of a specific disease

Affinity: chemical attraction

Agar: a solid jelly-like substance capable of supporting the growth of micro-organisms such as bacteria and fungi

Agency staff: hospital workers, e.g., nurses who are not employed by the hospital but are provided by an employment agency to meet short-term vacancies within the hospital

Ampicillin: an antibiotic of the penicillin group which is used to treat a wide variety of infections including chest, bladder and skin infections

Analogue: corresponding or similar to

Antibacterial policy: written guidance of the recommended antibiotics and their dosage for the treatment of specific infections

Antibacterial spectrum: the range of antibacterial agents to which a particular bacterium is susceptible

Antibiotic: a substance, produced by or derived from a micro-organism, which destroys or inhibits the growth of other micro-organisms

Antimicrobial: a drug which at low concentrations exerts an action against microbial pathogens and exhibits selective toxicity towards them

Antiseptic: nontoxic chemical often applied to skin to cleanse dirty wounds or to clean skin before an operation so as to prevent infection

Asymptomatic: not showing any symptoms of disease, whether a disease is present or not

Audit: organised review by staff of current practices and comparing these practices against predetermined standards. Action is then taken to rectify any deficiencies identified. Later the audit is repeated to see if the standards are now met

Bacteriophage: a virus that attacks bacteria. Each bacteriophage acts specifically against a particular species of bacterium

Bacterium: microscopic single-celled organism. Infections caused by bacteria include tetanus and cholera

Bank staff: a recognised list of available hospital workers who do not have regular employment but who are willing to work at short notice to fill any vacancies which may arise within the hospital

Blood cultures: samples of blood taken from a patient with a serious infection, such as meningitis. These samples are incubated in the laboratory to try and determine the bacterial cause of the illness

BSAC: British Society for Antimicrobial Chemotherapy

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CCDC: Consultant in Communicable Disease Control. This is a doctor, appointed by each Health Authority, who has a responsibility for the surveillance, prevention and control of infections in the community. Usually also the Proper Officer

CDSC: Communicable Disease Surveillance Centre. Part of the Public Health Laboratory Service and situated at Colindale, London. Responsible for the surveillance of infections in England and Wales. Co-ordinates the management of national outbreaks of infection

Cell envelope: the outside of a bacterium made up of cell membranes and the cell wall

Cephalosporin: a group of antibiotics effective against a wide range of bacteria. Used for treating many infections including skin, bladder and chest infections as well as meningitis

Cerebrospinal fluid: the clear watery fluid that surrounds the brain and spinal cord

Chemotherapy: the prevention or treatment of disease by the use of chemical substances. The term is sometimes restricted to the treatment of infections with antibiotics and other drugs

Chromosome: one of the threadlike structures in a cell nucleus that carry the genetic information in the form of genes

Clostridium difficile: a bacterium which can cause severe diarrhoea or enterocolitis. This most commonly occurs following a course of antibiotics which has disturbed the normal bacterial flora of the patient's gut

CME: Continuing Medical Education. A scheme for monitoring education among senior doctors in hospitals and general practitioners. Participation in approved educational activities gains credits. Doctors are expected to achieve an agreed number of credits per year

Cohort nursing: placing together patients with the same infection within an area of a ward to reduce the risk of the infection spreading. Often used when the number of infected patients is greater than the number of single rooms available for isolation

Colonisation: the ability of some micro-organisms to reside on living tissue but not cause disease, for example normal bacterial flora

Communicable pathogens: micro-organisms which cause disease and are capable of being passed from a person, animal or the environment to another susceptible individual. Also known as contagious or infectious diseases

Community: relates to those diseases or health services which occur outside of hospitals

Compliance: the degree to which patients follow the instructions for taking a course of treatment

Contaminants: usually harmless micro-organisms which may be mix or pollute pure cultures in the laboratory

DGH: District General Hospital

Diphtheria: an acute bacterial infection affecting the throat. Vaccination can protect against the disease

Disinfectant: a chemical that destroys or removes bacteria and other micro-organisms. Used to cleanse surgical instruments and surfaces of equipment or furniture

DNA: deoxyribonucleic acid. The genetic material of nearly all living organisms, which control heredity and is located in the cell nucleus

Empirical treatment: management of diseases, such as drug treatment, based on experience or observation rather than specific recommendations based on, for example, laboratory investigations

EMRSA: Epidemic methicillin-resistant *Staphylococcus aureus*

Enterococcus: a bacterium commonly associated with bladder infections as well as skin and wound infections.

Enterocolitis: severe inflammation of the gut especially the colon and small intestine.

Enzyme: a protein that, in small amounts, speeds up the rate of a biological reaction without itself being used up in the reaction.

Epidemiology: the study of the occurrence, cause, control and prevention of disease in populations.

Escherichia coli: or E coli. A bacterium commonly associated with a wide range of infections. including bladder infections and diarrhoea.

Formulary: a compendium often used in hospitals to list the drugs readily available for prescribing and sometimes indications as to what seniority of medical staff may prescribe individual agents.

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Fungus: a simple plant which lacks the green pigment chlorophyll. Fungi may cause simple infections such as thrush or athlete's foot. They may also cause serious infections in patients whose immune system has been weakened by disease or treatment.

Gene: the basic unit of genetic material which is carried at a particular place on the chromosome.

Genus: a category used in the classification of animals and plants. A genus consists of several closely related and similar species.

Glycopeptide: a group of antibiotics including, for example, vancomycin and teicoplanin, used for the treatment of serious infections such as those due to MRSA. Can only be given by injection.

GMC: General Medical Council.

Gonococcus: a bacterium which is the cause of gonorrhoea, a sexually transmitted disease

GP: General practitioner.

Gram's stain: a method of staining bacterial cells with coloured dyes to aid identification when viewed with a microscope.

Gram-positive: bacteria which by Gram's stain appear violet microscopically.

Gram-negative: bacteria which by Gram's stain appear red microscopically.

Growth medium: fluid capable of supporting the growth of microorganisms such as bacteria and fungi.

Haematology: the study of blood and blood-forming tissues and the disorders associated with them, for example anaemia and leukaemia.

Haemophilus influenzae: a bacterium which most commonly causes respiratory tract infections and meningitis. Some strains of H influenzae can now be prevented by vaccination.

Helminth: any of the parasitic worms including the flukes, tapeworms and nematodes.

HIS: Hospital Infection Society.

ICD: Infection Control Doctor. Usually a medical microbiologist who with the Infection Control Nurse forms the Infection Control Team. A model job description for a hospital infection control doctor is available from the Association of Medical Microbiologists.

ICN: Infection Control Nurse. A senior nurse with specialist training in infection control who together with the Infection Control Doctor forms the Infection Control Team

ICT: Infection Control Team. On a day-to-day basis the ICT comprises the Infection Control Doctor and the Infection Control Nurse

ICU: Intensive Care Unit

Immunocompetent: having normal immune responses, as in a normal healthy person

Immunosuppression: having impaired immunity due to disease, for example cancer, or treatment, for example steroid drugs or radiotherapy

In vitro: tests undertaken in laboratory apparatus for example test tubes, not in a living human or animal

In vivo: tests undertaken within a living human or animal

IT: information technology such as computers

Locally: used for the route of administration of a drug which is applied directly, or topically, to the part being treated, for example to the skin or eye

Macrolide: a group of antibiotics, including erythromycin, which can treat a wide range of infections especially respiratory and skin infections. Often used as an alternative to penicillins

MDRTB: multiply drug-resistant Mycobacterium tuberculosis

Medical microbiologist: a person who studies the science of the isolation and identification of micro-organisms which cause disease in humans and applies this knowledge to treat, control and prevent infections in humans. A model job description for a consultant medical microbiologist is available from the Association of Medical Microbiologists

Medical microbiology: the science of the isolation and identification of micro-organisms which cause disease in humans

Meningococcus: a bacterium which most commonly causes meningitis and septicaemia or blood poisoning

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Microbe: any organism too small to be visible to the naked eye. Micro-organisms include bacteria, fungi, viruses and protozoa

Morbidity: the state of being diseased. Whereas mortality is the state of death

MRSA: Methicillin-resistant *Staphylococcus aureus*

Mutation: a change in the genetic material of a cell, or the change this causes in a characteristic of the individual, which is not caused by normal genetic processes

Mycobacterium tuberculosis: a bacterium which is the cause of tuberculosis or TB

NEQAS: National External Quality Assessment Scheme

Non-pathogen: a micro-organism which may be grown from samples collected from humans but which does not cause disease

Normal flora: micro-organisms which normally reside on the skin, in the gut and in the mouth and upper respiratory tract of humans. They usually protect these tissues from diseases

Notifiable disease: a list of infections such as cholera, measles and food poisoning which doctors have a legal responsibility to report to the Proper Officer of their local Health Authority

Nutrient agar: a solid jelly-like substance made from basic nutritional ingredients capable of supporting the growth of many, but not all, bacteria and fungi

On-call: a rota of medical staff available to give help and advice during the evenings, weekends and bank holidays. Laboratory staff are also on-call for the examination of urgent clinical specimens during these hours

Out of hours: times when a laboratory is normally closed to routine work but can undertake emergency work by staff who are on an on-call rota

PACT: prescribing analyses and costs. A scheme by which general practitioners may have information about the frequency and cost of their prescribing and allowing them to compare their practice against that of other doctors

Parenteral: giving drugs by intramuscular or intravenous injection

PAS: Patient Administration System. Hospital computer records of patient's name, date of birth, address, hospital number, religion, etc.

Pathogen: a micro-organism that can cause disease

Penicillin: a group of antibiotics, such as ampicillin, which can treat a wide variety of infections. Can be given by mouth or injection. Some people have to avoid these antibiotics because they are allergic to them

Penicillinase: an enzyme produced by some bacteria which is capable of antagonising the effect of penicillin thereby making the bacterium resistant to treatment by this antibiotic

Peripheral laboratories: these are laboratories in district general hospitals away from large city-centre reference laboratories

Pertussis: or whooping cough. An acute infection, usually of childhood, which has characteristic spasms of coughing. Can be prevented by vaccination

PHLS: Public Health Laboratory Service [of England and Wales]. An organisation of 48 peripheral laboratories based in district general hospitals, and a central facility at Colindale in North London which houses the headquarters, reference laboratories and CDSC

Plasmid: an extrachromosomal portion of genetic material

Pneumococcus: a bacterium most commonly associated with pneumonia and meningitis. Vaccination is available to prevent infections due to many strains of pneumococcus

PPA: Prescription Pricing Agency

Progeny: offspring or descendants

Proper Officer: This is a person, appointed by each Health Authority, who has a responsibility for the surveillance, prevention and control of notifiable infectious diseases in the community. Usually also the CCDC

Prophylaxis: any means taken to prevent disease. For example vaccination against tetanus or measles or giving antibiotics when patients undergo procedures which put them at risk of acquiring an infection although they do not have an infection at the time of the procedure

Protozoa: a single-celled micro-organism, usually bigger than a bacterium, which may be free-living or parasitic. Malaria is caused by a protozoa

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Pseudomonas: a bacterium causing a wide variety of infections but most commonly associated with patients whose immunity is impaired by either disease, treatment or indwelling medical equipment and devices

QA: or quality assessment. Schemes whereby laboratories examine samples with known results to ensure that their testing methods are valid. Schemes may be internal whereby laboratories repeat tests on their own samples or external, e.g., NEQAS, when laboratories send samples to each other for testing

Reference laboratory: one which receives samples from other laboratories so that more specialised tests can be carried out. Usually also involved in research relating to their particular area of interest

Ribosome: a particle, consisting of RNA and protein, that occurs in cells and is the site of protein synthesis in the cell

Salmonella: a bacterium most commonly associated with diarrhoea and food poisoning

Soft tissue: usually refers to the tissues underneath the skin

Species: a group of genetically related micro-organisms having many features in common

Staphylococcus: a group of bacteria which cause a wide variety of infections especially those of skin and wounds. More serious infections include blood-poisoning; pneumonia as well as heart valve, bone and joint infections.

Streptococcus: a group of bacteria which cause a wide variety of infections including those of the skin and wounds. More serious infections include scarlet fever and pneumonia

Synthesis of cell wall: construction of cell wall

Systemic treatment: drugs given by mouth or injection

Target site: the specific part of a cell upon which a drug such as an antibiotic acts

Tetanus: or lockjaw. An acute infection affecting the nervous system. Infection occurs by contamination of wounds by bacterial spores. It can be prevented by vaccination

Tetracycline: a group of antibiotics effective against a wide variety of infections such as respiratory tract infections, acne and genital infections

Therapeutics: the study of the different methods of treatment especially the use of drugs in the cure of disease

Topically: used for the route of administration of a drug which is applied directly, or locally, to the part being treated, for example to the skin or eye

Toxin: any poisonous substance produced by micro-organisms

Treponema pallidum: causative organism of syphilis

Trimethoprim: an antibiotic most commonly used to treat bladder infections

Tuberculosis: or TB. An infectious disease most commonly affecting the lungs. Treatment with antibiotics takes many months. Vaccination with BCG will prevent many cases

Vaccine: a special preparation of material that can be used to stimulate the development of antibodies and thus confer immunity against a specific disease or number of diseases. Usually given by injection and started in early childhood. Can be used to prevent many infections including measles, mumps, rubella, whooping cough, hepatitis A and B and rabies

Virus: a very small micro-organism of simple structure only capable of survival within a living host cell. Influenza and measles are caused by viruses.

VRSA: Vancomycin-resistant, methicillin-resistant *Staphylococcus aureus*

VRE: Vancomycin-resistant enterococcus

WTE: Whole-time equivalent

Zone of inhibition: area around an antibiotic impregnated paper disc within which no bacteria have been able to grow due to the bacteria being killed by that antibiotic. Hence the bacterium is susceptible to that particular antibiotic which would then be suitable for treatment

Zoonosis: an infectious disease of animals which can be transmitted to humans, for example brucellosis and rabies

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Examination of witnesses

PROFESSOR DAVID REEVES, President, Association of Medical Microbiologists and Consultant Medical Microbiologist, Southmead Hospital, Bristol; DR MARK HASTINGS, Consultant Medical Microbiologist, Queen Elizabeth Hospital, Birmingham, DR RICHARD SLACK, Consultant for Communicable Disease Control, Nottingham Health Authority, and DR PAUL WRIGHT, Consultant Medical Microbiologist, Conquest Hospital, Hastings, of the Association of Medical Microbiologists, were called in and were examined.

Chairman

1. May I ask you firstly to introduce yourselves and then following that to explain the role of the medical microbiologist and to summarise the main points of your submissions, for which we thank you very much indeed; they are very comprehensive and informative.

(Professor Reeves) On my far right is Dr Mark Hastings who comes from Birmingham and is the Secretary of the Education, Science and International Affairs Committee of the Association. On my immediate right is Dr Richard Slack who works in Nottingham and is the Chairman of the Prevention and Control of Infection Committee of the Association. On my left is Dr Paul Wright who is the Editor of the Association's Journal and its Publications Secretary. If I could perhaps first go to the **role of the medical microbiologist**. There is a medical microbiologist either in or available to every hospital in the United Kingdom. Their duties are to run the diagnostic laboratory and advise in clinical circumstances on the diagnosis and therapy of infections. They lead the infection control team in the hospital which is responsible for helping to prevent infection, and many of them carry out research and teaching about antimicrobial therapy and prevention of infections. That in summary is what medical microbiologists do. I will briefly outline the evidence that we are going to present and say what we hope to achieve. There are many types of antimicrobial agent including anti-virals, anti-helminthics and anti-fungal agents but we would want to concentrate on antibacterials because we believe this is where the Committee's interest must lie. It is the main problem in the United Kingdom and it is the one that has grabbed everybody's attention at the present time. Bacterial resistance to antibacterials is rising inexorably. It has become of major concern around the world and in this country. It is of direct relevance to treating people who have infections and it threatens the utility of antibacterial therapy into the first decade of the next millennium. So maybe by 2010, if something is not done, we will be seriously impaired in our ability to treat bacterial infections.

The evidence we are going to present is structured into three sections. First of all, Dr Slack will talk about the basis of resistance which will hopefully increase your scientific understanding of the basis of resistance and its clinical impact. Also he will discuss problems in collecting the epidemiological data about resistance. Dr Hastings will then discuss the current role of the microbiologist in detecting and controlling resistance. This, I hope, will give you an understanding of the way medical microbiological services in this country are organised and how they impact on detecting and controlling resistance. Finally, I am going to review

the way antimicrobials are used in this country so you can have information about where action can best take place. I will look at suggestions as to how their usage can be improved and we will discuss many actions that could be taken to combat the trend in rising resistance. In conclusion, we would like to say that the problem is real, the actions to combat that problem are many faceted and I do not believe that any single action is going to be effective by itself. Some action should be commenced now if we are to have a chance of influencing resistance in the near and medium term and many of the actions which we may need to take are going to be difficult and painful to implement

2. With the documentation you have provided very useful information on how bacterial viruses acquire resistance and how they spread. It would be helpful to us to have a summary statement on that ending up with whether it is conceivable that there can be a drug that is irresistible from the point of view of bacterial infections.

(Dr Slack) As far as the definitions of resistance are concerned, there are in fact two basic types of resistance to bacteria: first, that which is inherently present, which is **primary resistance**, where bacteria are insensitive to agents at defined concentrations. It is perhaps worth reminding members that the definitions of resistance depend on the concentrations of agents attainable in the body and that drugs work by selective toxicity, by killing bacteria in concentrations in the human host. Examples that I have given of inherent resistance might be *E.coli* to penicillin or erythromycin. If indeed one uses high concentrations of those drugs in the laboratory you may kill *E.coli* but in clinical practice they would not be used for the treatment of infection by *E.coli*.

What is of particular interest to your Committee is "**acquired**" resistance, that is resistance where some members become more resistant than others within the same species. If we take *Staph aureus*, the common cause of wound infections in hospitals, some of those are sensitive to penicillin but the majority nowadays, over 90 per cent in hospitals, are resistant to penicillin. Similarly, erythromycin resistance in different communities varies and one can use that as a measure of the degree of resistance and sometimes that has been used as a measure to look at the amount of prescribing of a particular drug in a community and these are selected from the population.

On the basis of resistance one wants to say that there are inherent mechanisms and there are transferable mechanisms. The **inherent mechanisms** are that the antibacterial may not be able to penetrate into the bacterial cell to reach the concentrations required. It may not be able to attach to the target of action of the drug. There may, indeed, not be a specific target to that particular drug. **Acquired mechanisms** are again

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PROFESSOR DAVID REEVES, DR MARK HASTINGS,
DR RICHARD SLACK and DR PAUL WRIGHT

[Continued]

[Chairman Contd]

multi-faceted. That is one of the points we wish to get across: that antibiotic resistance is not a single problem, it is many different problems in different organisms. Some may be enzymes which destroy the drug, for example penicillinase, which is the common mode of resistance in *Staph aureus* as I mentioned before, and some of them alter the permeability of the drug inside the cell particularly in Gram-negative organisms. There may be reduced affinity and in some cases this resistance can lead to increased expulsion of the antibiotic from the cell and there may be production of a different target site which is not sensitive. It is producing a false target and in that way cheating the antibacterial so that it cannot work.

3. Are these in order of importance?

(Dr Slack) I think that is a difficult question to answer because it depends on the different species. As far as staphylococci are concerned and as far as *E.coli* is concerned the enzymes that destroy antibacterials, the beta-lactamases, are some of the most widely prevalent found in medical practice so in that regard those would be top of the list.

4. Thank you.

(Dr Slack) It is important to recognise that within a population of bacteria there will be quite a wide variation of resistance. If one were able to pick a single cell and determine what its resistance would be, within that population there is a distribution of resistances. This is phenotypic variation or phenotypic resistance and may be seen in different stages of growth of the organism: in older cultures and where they are in a more latent phase (or in a more quiet phase) they are less sensitive than in the rapidly dividing organisms, so there is a variation of that.

Also there is acquired resistance. There may be two main mechanisms, mutation of chromosomal DNA and acquisition and transfer by plasmids. Plasmids are small pieces of DNA which code for the resistance and they particularly have the ability to self-replicate (that is they do not need the division of the whole bacterial cell to produce more) and they are easily transferable from one bacterium to another both within species and also across bacterial species. Transmission is largely by three routes. Conjugation is a form of sexual intercourse between bacteria where the donor injects the DNA through a narrow tube which links the bacteria together which is commonly seen in *E.coli* and other coliform bacteria. Transformation is a system where naked DNA may be taken up from the cell by live bacteria. This was first described in pneumococci and is also probably important in some other organisms. Transduction is where bacteriophages, which are viruses which may infect bacteria, can carry the DNA between cells. A bacteriophage can infect another cell and carry with it on its DNA the resistance genes to confer that resistance.

Lord Winston

5. Genetic conjugation: is it just the plasmid that is transferred or can you have bits of DNA as well?

(Dr Slack) The plasmid is the bit of DNA that is transferred but on that plasmid there may be many

different determinants. There may be not only the resistant genes but there can be many other genes as well. Transposons are, in fact, DNA which can be transferred from the plasmid onto the chromosome itself and they then become incorporated into the bacteria cell and can then replicate throughout the existence of that cell.

We would like to get across also what happens in the laboratory in the **testing of the sensitivity or resistance** to antibiotics. Most laboratories use either solid culture media or liquid to determine the response of the growth of bacteria to the antibiotic. When one thinks that a patient is infected with a particular organism one would take that organism and try to determine its sensitivity to a range of antibiotics. Often in the literature you will see the term MIC (minimal inhibitory concentration) which is a concentration of antibiotic which prevents bacteria growing in those artificial conditions. It is therefore an artificial term, a laboratory term, and laboratories then report on this as sensitive to penicillin or resistant and that means there is a level of resistance which we believe correlates with the response in patients to a course of antibiotics. What, of course, is important is, does this correlate?—*In vitro veritas?* as one of my colleagues, David Greenwood, wrote in the *Journal of Infectious Diseases* (1981, 144: 380-385). There are of course many problems in this correlation between the resistance found in the laboratory and the response to antibiotics in the patient, one of which is that many infections are self-curing. For example, urinary tract infections in young adults very commonly, maybe 50 per cent of them, will spontaneously cure themselves or with fluids will do so. On the other side there may be patients who have impaired body defences who do not respond to antibiotics even though it appears that they may be sensitive in the laboratory. There are also problems with different antibiotics in different body fluids in that concentrations of a drug may vary greatly. For example, in urinary infections high concentrations of antibiotic are found in the urine so if the tests that are done in the laboratory do not take account of that it may appear they are resistant to ampicillin but in fact such high concentrations of the drug are found in the urine that the bacteria in the urine are killed. The aim generally in systematic infections, that is infections within the body cavities, is to find a concentration of antibiotic at the site of infection which is between two and eight times the MIC. Again there is some data to support this in the literature. The correlation between the MIC and the success or failure of treatment is often difficult to find because most infections are overtreated rather than undertreated, but in acute gonorrhoea there has been in the literature in the past good evidence to correlate between (on the bottom line of figure 1 of our memorandum) the MIC, that is the minimum inhibitory concentration, to penicillin which to the right of the figure is increasing. Thus on the right they are highly resistant organisms, on the left they are highly sensitive. Groups of patients were treated at the London Hospital in the 1950s when penicillin resistance was increasing in gonococci and the dose of penicillin that was given, the standard dose, was we would think nowadays rather low because

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those concentrations have increased very much because of the recognition of resistance of gonococci. On the upper axis I have put the percentage of treatment failures. One will see when the MIC reaches 0.3, ie the organism is resistant, then 100 per cent of patients failed. This is a single dose in acute gonorrhoea in men which is otherwise a very easy treatment and an easy treatment to monitor because specimens can be taken very easily. The highly sensitive strains would be low MIC, less than 0.02, which were all cured by this single dose. There are other examples in the literature. What I think is clear in this example is the correlation between resistance and clinical practice.

I would like now to talk about the **epidemiology of resistance and the collection of data** about it. Why do we want to know about the epidemiology of resistance? There are two main things. One, we need to know if we have got anything really unusual in the situation. For example, I am sure you have heard about methicillin-resistant *Staph aureus* and in Japan there has been the finding of vancomycin-resistant *Staph aureus* which are almost untreatable bacteria. We would also be horrified to learn if there was penicillin resistance to meningococci, the commonest cause of bacterial meningitis. More commonly we need to know what is the rate of resistance in a clinical setting because this can be used to aid us in producing antibiotic guidelines for practitioners. We may, for example, want to know how many patients have got MRSA in a hospital and how many of a particular strain of organism, for example *E.coli* in urine might be resistant to ampicillin and there is a degree of literature on this. If resistance reaches above a certain level then one might change the guidelines for treatment. We collect information routinely in an unstructured way and the point we would like to make to you about the epidemiology is that laboratories do not at present have to report nor do they routinely collect information on antibiotic resistance. The notification of some infectious diseases is through the Public Health Act 1984 and the Infectious Diseases Regulations 1988. A White Paper will be produced in the next month or two by the Government to look at a change in the law of notification of diseases but laboratory reporting at the moment is voluntary. There is a proposal that this might be made a statutory requirement but antibiotic resistance is not notifiable by these routes unless the organism is one of the notifiable infectious diseases such as tuberculosis and we have good information on the amount of drug resistance in tuberculosis in the United Kingdom but not about anything else. What we would like to propose is that there is some systematic collection of information of antibiotic resistance. The variables, as you may well imagine, my Lord Chairman, include the fact that not all patients go to their doctor. There may be many infections that are therefore missed. Many doctors do not take specimens from the patients and the laboratories may not isolate the cause of their infection. There are also many variations in the way laboratories do resistance testing and the definitions used and, as I said before, they may not be reporting that centrally in this country.

My last point is the **clinical consequences of resistance**. In many cases there is empirical therapy because we do not know in most cases the antibiotic resistance of the organism because it may take 48 hours or longer before this is found out. Thus many patients are treated empirically. This leads really to our role in producing guidelines and producing protocols where practitioners can use the most appropriate drug for those circumstances and there are, of course, consequences of this in terms of the development of antibiotic resistance. The other factors that are important on the list in our memorandum in terms of the consequences of resistance are that where there are multi-resistant organisms, where it may be necessary to use intravenous not oral drugs or it may be necessary to use more toxic drugs, there may also be super-infection with some pathogens that are resistant to all agents. Antibiotic resistance also has an effect on increased hospital stay and means that sometimes less effective drugs have to be used rather than the optimum ones; and because resistance determines on the degree of cross-infection it may well be that there needs to be more use of patient isolation facilities.

Lord Gregson

6. I cannot reconcile the use of the word “mutation” as against “natural selection” because I have seen no evidence of an actual mutation being presented in the various papers I have read. I am not a medical scientist, I am a radiation sort of bloke and I can recognise radiation mutation because it is a single generation effect but it looks awfully certain to me that you have natural selection taking place rather than mutation and the use of the word mutation somewhat discolours the picture.

(Dr Slack) My Lord, I think you are right, that what we are talking about is the selection of mutations that are occurring naturally.

7. Are they mutations or do they already exist?

(Dr Slack) I think they are occurring spontaneously. As bacteria divide, maybe in the order of $1:10^9$ there will be a mutation or an alteration to the chromosome.

8. But the rate of breeding, if you like to take that term, you are not talking about a single generation, you are talking about multi-million generations in terms of reproduction and so forth, thus the rate of natural selection must be enormous.

(Dr Slack) Bacteria multiply in optimal conditions every 20 minutes and there may be millions of generations over our lifetime.

9. Billions over our lifetime!

(Dr Slack) And natural selection would therefore operate much more quickly than it would in human genetics and I think we are seeing selection of those naturally occurring mutants. For example, in the treatment of tuberculosis, if you use a single agent like rifampicin you very quickly get resistance because it is known that there are natural resistance mutations to that at the rate of $1:10^9$.

Lord Gregson] You are using the word “mutant” there but it is not mutation in my definition.

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Lord Dixon-Smith

10. I am trying to get the definitions correct. If I understand matters correctly, when penicillin was first introduced there were already resistant bacteria in place so a not unreasonable assumption would be that those resistant strains by a natural selection process become increasingly prevalent. Is there any evidence that the nature of resistance has changed which might actually suggest mutation rather than genetic inheritance or natural selection?

(*Dr Slack*) I am not sure that we have enough stored material to be able to say whether all the resistances were present pre the antibiotic era. I think natural selection is the most important operator but that bacteria are constantly mutating and where there is an increased selection pressure by antibiotics then one will select out those mutants that are occurring spontaneously in the population.

Lord Rea

11. Bacterial cells multiply much more rapidly than cells in our body for instance, but do mutations take place at about the same rate with regard to the number of generations of each cell between each mutation?

(*Dr Slack*) I do not know the answer to that, I am sorry.

Lord Walton of Detchant

12. Is it then the case that some mutations in the bacterial DNA confer resistance which had not been present previously?

(*Dr Slack*) Yes.

Lord Walton of Detchant] In other words, that is one factor in the development of resistance which is quite different from the natural selection of organisms which were primarily resistant. Lord Winston] Chairman, surely there must be techniques such as the polymerase chain reaction so you can test a sample of a bacteria at the start and see whether or not a particular mutation is present and then decide whether or not it is present at the end of treatment. Is that not so and, if so, can you therefore detect mutations and knock this on the head?

Lord Dixon-Smith

13. Presumably mutation is random and susceptible bacteria become resistant but equally over time presumably some resistant bacteria might well mutate and become susceptible again, although they would be swiftly swept up by the treatment if that were the case.

(*Professor Reeves*) You are absolutely right in that you have spontaneous mutation going on in bacteria all the time as they divide and mutations occur randomly and at different rates according to which form the mutation is. In the absence of any selection pressure many of these mutations are disadvantageous. For example, if you changed a target site of a particular antibiotic that might make that chemical process slightly less efficient within the bacteria. These cells

may grow more slowly and therefore in the absence of a selection process you would tend to get a reversion back to a fully sensitive population and it is the combination of mutation and selection pressure which has led to the selection of resistant mutants.

Lord Phillips of Ellesmere

14. Would it be worthwhile looking in a little more detail at penicillin resistance to illuminate this problem. Penicillin acts by inhibiting the enzyme which constructs the bacteria cell wall, putting it loosely. There is an enzyme, beta-lactamase, which attacks penicillin. There is structural evidence that beta-lactamase has evolved from the enzyme that constructs the cell wall. They are structurally rather similar. Penicillin, as we know, is a naturally occurring product so it is not at all improbable that out in the natural world some bacteria will have protected themselves against penicillin by a process which involves a doubling of the gene, let us say, so there are two copies of the gene that make the bacterial cell wall, one of these copies mutates and turns eventually into the gene coding for an enzyme which destroys the penicillin. That would suggest, as we know, that beta-lactamase existed in nature before the use of penicillin as an antibiotic and it came about by that sort of process. Is that not right?

(*Professor Reeves*) We know that because people had cultures from the 1930s freeze-dried and some of these cultures produced beta-lactamase.

Lord Gregson] That, my Lord Chairman, is the definition of "natural selection" starting with Darwin!

Lord Phillips of Ellesmere] Natural selection is a process working on mutants.

Lord Perry of Walton

15. Maybe they are present beforehand or maybe they arise during the treatment.

(*Professor Reeves*) Can I just make one other point: it is not just mutants where natural selection is important. It can also select bacteria which is inherently resistant to certain antibiotics. If you have a bacterium that is naturally resistant, all the members of the species are resistant because of the physiology of that particular species and you put on a big selection pressure particularly in hospitals where you will actually select those sorts of infections. A good example is the widespread use of cephalosporins which has increased the number of enterococcal infections, which are resistant to cephalosporins, so you get both effects.

Chairman

16. Embedded in one of Lord Gregson's questions is, where do these resistant organisms come from and what is the contribution from different areas such as human medicine, animal medicine and the use of growth promoters and things like that in the animal feed industry? Have you any comments on that?

(*Professor Reeves*) I have some comments in my evidence later, my Lord Chairman.

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17. You would rather hold that at present?

(Professor Reeves) If that is all right.

Chairman] Lord Gregson, have you any further points you would like to make?

Lord Gregson] No. I am utterly confused!

Baroness Platt of Writtle

18. As a matter of bacterial ecology, what is the relationship between resistance in the hospital and resistance in the community?

(Dr Slack) There is obviously a complex relationship between the two. There is resistance within the hospital which is selected. For example, if one takes MRSA, that is selected for in the hospital but often it is found that it has transferred into the community as patients go into nursing homes particularly. It has come from largely being a hospital problem to now being very much a problem in the community as well. For organisms such as I was describing, E.coli or salmonella, problems which are largely in the community sphere, those organisms also come into the hospitals and may cause problems there.

19. I have read your paper and it is full of infection control within hospitals but, of course, you are not getting the same infection control in the community.

(Dr Slack) Absolutely and I think that is one of our concerns that these multi-resistant organisms are now a community problem and have now spread within the community.

Lord Jenkin of Roding

20. I am Chairman of an NHS trust which suffers from MRSA in that many of the patients that come in are, as it were, carriers where they are do not suffer an infection but have organisms about their person. When you are talking about community infections are you talking about people infected with MRSA as opposed to those who happen to have it in their bodies?

(Dr Slack) I am talking about both situations, both those infected with it and those carrying it on their bodies. There is an increase now in the community of both situations, and particularly those that are not infected that are carriers are found in the community and Professor Reeves has some evidence of this from studies that are going on.

Lord Dixon-Smith

21. I have a little difficulty with this question of "infected". Presumably there is no distinction between people who are infected who have not got a problem and people who are infected and have got a problem. They are both infected, but some are infected to a level producing a clinical condition and some are infected to a level which does not cause them any problems. Perhaps they have resistance.

(Professor Reeves) It would be better if one used the terms "infected" and "colonised" which means you have the organism but it is not causing clinical

disease. Those are the terms we tend to use to make that distinction.

(Dr Hastings) When you talk about MRSA, methicillin-resistant Staph aureus, you have to understand that about a third or half the people in this room will be colonised with Staph aureus and it is the carriage of the resistance gene which is the worrying factor.

Baroness Masham of Ilton] Chairman, on the point Lord Jenkin made about the infection coming in from the community, there was a recent case in Northallerton where it is thought that E.coli came in from a patient and infected people including staff in the hospital and two people died. That is in the last few weeks.

Baroness Platt of Writtle

22. Infection control is obviously stronger in the hospitals and I notice you carry out training within the community but where you have this interaction, which is clearly very important, how do you bring your infection control from the hospital into the community?

(Professor Reeves) Very many of the infection control teams within the hospitals have nurses who also work in the community, in other words it is part of the team's remit. This does not apply to all of them because of resource constraints but where you have enough infection control time within the hospital people do look outwards into the community because as an infection control team one realises that you have this "revolving door" with infection going out and coming back in again. Certainly a lot of infection control nurses put a great deal of effort into going out into the community and nursing homes and talking about infection control problems that need resolving. So it not an area that is ignored but, unfortunately, with the amount of infection control resources one has in a hospital it is quite difficult, particularly if there is a big problem in the hospital, to spend a lot of time in the community. We probably spend less time there than we should.

*Lord Walton of Detchant*23. Are there scientific techniques available at present to **reduce the levels of resistance** in organisms and would the answer be different for different organisms? There was a report in August in the *New Scientist* suggesting that antibiotic resistance genes can be disabled by "antisense" or "external guide sequence" techniques. On the other hand, a report in the *New Scientist* in September said that in the absence of antibiotics resistance does not necessarily evolve away. In the absence of antibiotics does it ever evolve away or reduce spontaneously?

(Professor Reeves) The most important factor in maintaining resistance is selection pressure and there is plenty of evidence that if you remove the selection pressure the organisms will slowly revert, some types of organisms more quickly than others, and to certain antibiotics more quickly than to others. Ultimately any bacterium which is producing a mechanism to resist

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the action of an antibiotic in the absence of that antibiotic is putting itself at a biochemical and physiological disadvantage because it is subverting part of its mechanism to do that. Ultimately, if you reduce antibiotics of course the resistance will go away. There is a very nice study in Finland about reducing the use of macrolides and increasing the sensitivity of streptococci. That was a nationwide initiative in Finland reported only in August.

24. May I follow that up by asking you to comment on the **future of antimicrobial therapy**. I was intrigued, for instance, to read of developments described by some cellular microbiologists working in a dental hospital. They talked first about light-induced antimicrobial agents saying that low-powered lasers could generate bacterocidal molecules. They went on to talk about the possible development of antimicrobial peptides and commensal-bacteria interactions producing what they call bacteriocines and also talked about cytokine blockade. What do you feel about these prospects because many people tell us that they do not see any new antibiotics of a conventional kind emerging from research in the next few years.

(*Professor Reeves*) I feel that every avenue needs to be explored. This is such a serious situation that we cannot afford to ignore leads and each of these leads should be properly explored and evaluated. I have to say that many of them might be very difficult to deliver as antibacterial therapy in the end because, although you can get things to work in a test tube, at the end of the day you have got to give them to people and the actual delivery might be a problem. The treatment might be unstable in the body, it might be toxic or it might be insoluble; all sorts of things. Laser activation might be fine in the mouth but it would not do too well if you had an endocarditis! There are huge problems in ultimately delivering innovations as a viable treatment but, nevertheless, we should not close our minds to them at this stage, and we need to invest more in trying to improve the armamentarium.

Lord Phillips of Ellesmere

25. At a rather simpler level than using antisense DNA, it is of course possible to inhibit enzymes like beta-lactamase and there are number of inhibitors in clinical use in combination with penicillin or cephalosporins. Has that vein been mined adequately, do you think?

(*Professor Reeves*) It has certainly been quite heavily mined in the case of beta-lactamases but the bacteria seem very adept at producing beta-lactamases which are insensitive to the inhibitors. Not all beta-lactamases are inhibited by the inhibitors currently available so the problem with that is, if you use them intensively in the hospital, you select out resistant strains.

Lord Porter of Luddenham

26. We would like to hear your views on the **future of research** in resistance to antibiotics. From the point of view of understanding it better and then

of course, as follows from understanding, mitigating the problem, what are the key areas that you see having to be attacked in the near future?

(*Professor Reeves*) My Lord, I think the most important thing is that we actually continue to work to do rather basic research in the area of antimicrobial resistance. Unfortunately, resistance as an issue and antimicrobial drugs in general have become rather unfashionable in scientific circles and other things have tended to displace them in a grant-getting capacity, so it is actually quite difficult at the present time to get good grants to work on antimicrobial therapies and, for example, basic mechanisms.

27. Could I ask why you think they have become unfashionable? Is it because they are not working and people do not see a future for them?

(*Professor Reeves*) I cannot answer obviously for the grantors but I suspect that it is because they see more excitement in other areas.

28. Something more novel?

(*Professor Reeves*) More novel, yes. The other problem is that a huge amount of research, quite basic research, is done in the pharmaceutical industry, and indeed almost all the agents that have ever been developed, apart from one or two, came from the pharmaceutical industry. It has become commercially very unattractive now to do research into antimicrobial agents because the chances of getting a success from it are rather small, and so many companies have moved away into other forms of pharmaceutical endeavour.

29. Are there any antimicrobial agents which are really novel, different agents altogether, away from the brothers and sisters and sons and daughters of penicillin?

(*Professor Reeves*) Yes, people are developing new agents or trying to do this. The pharmaceutical industry has been trying to do that.

30. But something quite different, not chemical descendants of penicillin?

(*Professor Reeves*) No, there is a group of agents which I can never pronounce properly, oxazolidinones, which are in development. They are completely novel with regard to their mode of action and so on, such as is known about them.

31. Is this not then grant-gaining research? Is that not novel enough for the powers that be?

(*Professor Reeves*) I think it is very difficult for people to compete against. If a company decides that it wants to develop something like that they will probably do better than most academic researchers because they can switch huge resources into it and you will be left behind. I have to say these agents are not looking terribly promising at the present time in therapeutic terms.

32. So the academic research would be into the basics of it and it is hard to get grants even for the basic research?

(*Professor Reeves*) I think that is true.

(*Dr Hastings*) I think it is a lot more difficult than it was, say, 20 years ago.

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Lord Porter of Luddenham] Compared with other areas of microbiology.

Lord Gregson

33. Are you talking about non-government grants or government grants?

(*Professor Reeves*) I am really talking about Wellcome and MRC and the major granting bodies.

Lord Winston

34. Dr Slack, you alluded to the ability to make a diagnosis of specific sensitivity within 48 hours. Clearly one of the issues is the spraying of antibiotics on bacterial infection that may not be susceptible to that antibiotic. Do you see any progress being made in being able to **speed up the process of diagnosis** of specific sensitivity to a given antibiotic?

(*Dr Slack*) I think that is an area where we do see more progress being made. I think one of the other areas of research development which could be taken up much more by the NHS is in improving microbiological diagnosis and in promoting guidelines and research into the effective use of antibiotics. As far as rapid methods are concerned, there are indeed many new novel techniques for making a microbiological diagnosis and that can also show the resistance fairly quickly. One of the problems with some of them, of course, if they are looking for a specific gene sequence, is that it may not actually be expressed in the bacterium. For example, one could say that you could find the resistant gene to beta-lactamases but it may not be being produced in sufficient quantities to make any difference to the infection, i.e. there is not enough beta-lactamases there to remove the ampicillin or penicillin.

Lord Jenkin of Roding

35. You mentioned just in passing the Wellcome Foundation. One of the facts which always surprises people is that there is more medical research financed by the charitable sector than by the MRC. One can understand the pressures on the MRC, but do you think it would be helpful if this Committee specifically drew the attention of some of these broad spectrum charities to this fact and said, "Here is a real problem, there is a need for more research"? It has become unfashionable for whatever reason. Do you think we should ask them to look at this a great deal more intensively to see if they could help?

(*Professor Reeves*) Yes.

Lord Walton of Detchant] Should we not also ask the ABPI why it is unattractive to the pharmaceutical industry at the moment when one looks back to see the enormous profits they made out of the cephalosporins, for example? Any major antibacterial agent I think would be a very great success and a very great profit-spinner.

Chairman

36. I am conscious that Dr Hastings has a presentation to make.

(*Dr Hastings*) My role is to outline the **role of the consultant medical microbiologist** in infection and

microbiology services in the United Kingdom, and how that role relates to antibiotic resistance, and I will finish on some of the difficulties we are facing at the moment in our role and how that impinges on controlling antibiotic resistance. Three of us belong to the medical microbiology fraternity. There are 564 medical microbiologists practising in the United Kingdom.

Baroness Platt of Writtle

37. What about Scotland?

(*Dr Hastings*) Of the 564, 293 are NHS consultants. In England and Wales that is supplemented by another 161 who work for the Public Health Laboratory Service and there are 110 who work in academic institutes of medical microbiology. If we relate that to thousands per population, there is almost one microbiologist per 100,000 population. There is some variation between regions and the Scots as ever are doing better than everybody else. There is one microbiologist per 71,000 there as opposed to Northern Ireland which is not doing so well because they have only got one per 115,000. We do not really have any hard evidence that these differences have made any difference in practice or outcome.

38. Scotland does not have the Public Health Laboratory Service either, is that correct?

(*Dr Hastings*) It is only England and Wales.

39. What happens in Scotland?

(*Dr Hastings*) They have a slightly different system.

(*Professor Reeves*) They have their own communicable diseases central function rather like the CDSC at Colindale and all the laboratories in Scotland are funded to provide epidemiological data to that central service.

(*Dr Hastings*) We belong to a team of people who are looking after infection microbiology services. We are not too humble to suggest we are the pivotal person within this team. We have both a laboratory role and a clinical role. In our laboratory role we interact with clinical scientists and biomedical scientists in providing the diagnostic service which includes antibiotic susceptibility testing. On the clinical side we have a role in controlling infection and we interact with infection control nurses and with CCDCs (Consultants in Communicable Disease Control), of which Dr Slack is an example, who have a primary role in controlling infection within the community and who have a public health and infection background.

Most consultant medical microbiologists have come up through the following training pathway. As junior doctors we decided to do microbiology and joined the ranks of what are now called Specialist Registrars in Microbiology under the new Calman training scheme. As a specialist registrar you had a fairly varied training including experience in clinical infection, in infection control and in management, but one of the core areas we are trained in is in science of microbiology and this includes the science of antibiotics and the science of antibiotic resistance. So we have strong laboratory training. That is reflected in our MRCPATH exam which

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includes a three-day practical exam. So we do have a strong laboratory base although at the same time we have a lot of experience in clinical infection and infection control.

As to what we actually do on a day-to-day basis, normally the consultant microbiologist would be the director or the manager of a lab. In that role he will obviously have responsibilities regarding financial control, safety, personnel matters and so forth. But in terms of what we are talking about today it is worth reflecting that it is the consultant head of laboratory who has direct responsibility for the accuracy and the quality of the results that come out of that laboratory. In terms of input into that result, our main role is interpretation, and diagnostic microbiology is a very interpretative science. Swabs and various specimens that come down into the laboratory provide us with a whole host of organisms which grow, some of which are normal flora (colonizing bacteria), others which may be pathogens causing infection. It can be quite difficult to interpret what is going on from individual specimens so there is a lot of interpretation needed. As a clinical microbiologist part of your role is to devise protocols which allow this interpretative aspect to be layered on to the basic isolation of organisms. There is also a need for day-to-day interaction with the biomedical scientists who are isolating the organisms and indicating what is important and what is not. Most of us now would spend perhaps 25 per cent of our time on the wards interacting with clinicians, and visiting certain areas of the hospital on a regular basis, intensive care units, special care baby units and so forth. This is to give advice on diagnosing and treating infection. We also have a major role in infection control. The consultant microbiologist will normally be the Infection Control Doctor for the Trust and would normally chair the Infection Control Committee. On an every day basis he would be working closely with the Infection Control Nurse dealing proactively and reactively with infection control problems. Finally, but not least, teaching and research. Although we always think of teaching and research as being something for the academic institutes, the consultant microbiologist in the district general hospital is continually teaching on a day-to-day basis, teaching various health care workers about the importance and practice of infection control and of microbiology in general. It is much the same with research. In the past a lot of important research into microbiology—it may not be blue sky research, it may not be very fundamental—has come out of district general hospital microbiology laboratories. If I could then go back to this role but perhaps emphasise the role in relation to limiting antibiotic resistance. Within the laboratory we do not test all organisms for sensitivity to antibiotics; it is selective testing. One of our roles is to indicate which organisms should be tested and what should not. We also selectively report. We do not tell the clinician every antibiotic sensitivity result. We restrict the information we give clinical colleagues to help to control the use of antibiotics. We have an important role in maintaining quality both internally and through external quality assurance schemes. We have an important role in providing local

and national epidemiology in terms of antibiotic resistance. We also have a role in advancing practice. There are new antibiotics, and there are new ways of testing antibiotics for resistance. We have to take all of these on board. In terms of our clinical interaction, we play a pivotal role in writing the hospital antibiotic policy and in helping to audit the use of antibiotics within the hospital. On an individual basis we give advice on a daily basis on antibiotic use. We provide resistance data to clinicians, particularly to general practitioners, helping them to select the best antibiotic to use, guiding them to a sensible choice. We also have a role in assessing new antibiotics and whether they ought to appear on our own hospital formulary or should be used by local general practitioners. I glanced at an old BNF (British National Formulary) I found in my office before I left and I saw that in 1977 there are 18 antibacterials listed and in the current one there are 85, so it is an important task trying to guide clinicians into sensible use of these antibiotics. In infection control, as I have already indicated, we have both a proactive role (in terms of antibiotic resistance, that might be monitoring for resistant organisms within the hospital) and a reactive role, where we help to control antibiotic resistance spread by isolation of patients. Education and research, again as I already pointed out, is very important even in the district general hospital. We have an important role in research into the epidemiology of resistance and the appearance of new antibiotic resistance patterns.

Finally just to reflect on some of the pressures that we now have which are causing us problems in controlling antibiotic resistance. In hospitals laboratories are often seen as non-clinical areas and are very much in the front line of hospital cuts when financial directors are looking for ways of keeping within budgets. This has meant a reduction in staffing. My own laboratory has seen a 20 per cent reduction in biomedical scientists in the last four years. This is against a background of an increasing workload. My own hospital lab has seen an increase of five per cent per annum over the last five years and this is due partly to changes in medical practice, new infections, and the discovery of new techniques for detecting infections. Changes in medical practice include the increasing percentage of patients who now have indwelling devices which often become sources of infection, and more intensive care units. When I started in my hospital seven years ago we had nine intensive care unit beds; we now have over 20. This creates a lot more work in terms of infection problems and in terms of infection investigation. How does this affect us in terms of resistance to antibiotics? Many laboratories are now having to fall back on a core service. We have much less opportunity to take part in developmental work, in epidemiological work, applied research. We are having to concentrate on providing an every day core service. The other area where we face a problem is **infection control**. Efficiency and very high bed occupancy have become important bywords. Although we as health care professionals support the need to reduce wastage we do feel that we are beginning to lose the flexibility to operate a workable infection control policy. When you are faced with several patients carrying

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multi-resistant bacteria the first thing you want to do is to create some space.¹ Florence Nightingale taught us the importance of space between patients in terms of spread of infection. It is difficult to create that space any more because of this high bed occupancy. So from having two patients colonised you end up with half the ward colonised and then you cannot close the ward and so the organism spreads and becomes endemic in the hospital. It is compounded by increased patient movement. It is difficult to find patients sometimes nowadays as they are shunted from ward to ward so quickly to find an empty bed. There is also a lot of pressure to keep wards open. It is very difficult to close them. There is also a pressure on domestic services. It can be difficult even to clean thoroughly a bed space in between patients. It is compounded by lack of isolation facilities. Many United Kingdom hospitals have very few separate rooms where we can put patients who are colonized or infected by multi-resistant organisms. I am sorry, my Lord Chairman, to finish on such a negative note but I think it is important you understand some of the problems we face because it is important in how we combat the spread of anti-resistant organisms particularly in hospitals.

Lord Rea

40. We would like to know how you feel about the **costs and consequences for the Health Service**. We have already had some mention of the things which cost money and perhaps where we should be spending a little bit more money.

(Dr Hastings) Could I deflect that slightly because I know Professor Reeves has got some slides which directly address costs?

41. Yes.

(Dr Hastings) You are quite right, the acquisition of resistant organisms in hospital and infection arising from being in hospital, so-called nosocomial infection, does add on costs quite considerably and there are figures on that and Professor Reeves will show you them.

Baroness Masham of Ilton

42. My experience has shown that a terrible wastage to the National Health Service was the cost of patients having to sue for enormous amounts of money and if only there had been more isolation beds they might not have got an infection. Your point is very important, it is such a waste.

(Dr Hastings) At the moment there are cases of patients suing health authorities for becoming infected with multi-resistant organisms and you are right, there is knock-on waste because Trusts must now take on their own medico-legal cases. Sometimes hospital managers and finance directors do not always see it that way though. That is the next finance director's job!

(Professor Reeves) There is an appendix to the document and in it there is some parochial data from my own hospital which shows the impact of MRSA and I quote a couple of costs in there. That is just the tip of the iceberg because one had the tremendous task of trying to control the infection by cohorting patients on wards and losing bed space, and so on. It is very difficult to add up all these costs, but they are absolutely enormous.

Lord Rea

43. Do you think that spending money on the sort of things which Dr Hastings said were lacking would actually help us to save some of these costs which you mentioned in your appendix?

(Professor Reeves) I certainly think that some of the problems in **controlling infection in hospitals** stem from the pressure under which most hospitals now run. Hospital staff, particularly the nurses and the domestic staff on the wards, are under such pressure that have high levels of absenteeism and then you have to fill the gaps by getting in agency nurses who are not necessarily well versed in the infection control practices of your institution. It is actually extremely difficult now to control infection. Dr Hastings also mentioned the fact that patients are often housed on as many as three wards during the course of a really quite short stay in hospital because of the difficulty of finding appropriate beds for them. If they are carrying infection they may move once or twice before you realise they are infected, so the sort of pressures we are working under does compound the situation enormously. We do recognise that to correct those would cost a great deal of money to the National Health Service.

Baroness McFarlane of Llandaff

44. In one of the pieces of evidence we were given we were told that **nursing homes and residential homes** are now refusing patients with MRSA. Is that a knock-on cost in turn to the Health Service because in the end the Health Service has to take them back?

(Dr Slack) It is indeed a problem, though this has been addressed by the Department of Health to some extent in issuing guidance through our own professional organisation about MRSA in nursing/residential homes and meeting with the homes and particularly with the large insurance companies that insure homes to try to alleviate that problem. In spite of those measures there are still delays in admitting patients to nursing homes and indeed, they stay longer on the hospital premises and therefore are using the resources and blocking beds that could be used by other patients.

Chairman

45. Professor Reeves, I understand you have a presentation.

(Professor Reeves) I am going to talk about the actions we might take to try and control resistance in the future. I thought I would first review **the way we**

¹ Note from witness: i.e., infection control teams try to isolate and "cohort nurse" the patients, to prevent spread.

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use antimicrobials because it is important to one's understanding about where you might apply some of the control measures. In the developed world approximately 50 per cent of antimicrobials go into animal husbandry and only 50 per cent into humans, and that is an extremely important figure that people should bear in mind. The other thing which I have thought about is reducing the legitimate human use. I do not think anybody really suggests that we are going to give up using antibacterials. People have infections which should legitimately be treated. The real question is how much of that treatment is totally justified and how much is unjustified, and there may be something in the middle. It is extremely difficult to find this out because we do not have data on it. I have spoken to a number of microbiologists and we feel that by putting enormous effort into education amongst prescribers one might reduce the prescription use of antibacterials by about 20 per cent, perhaps as low as five per cent. They are the sort of estimates I have been given by people. In other words, some 80 per cent of the use of antimicrobials is fully justified and no one is suggesting that you are not going to do that. You have to then ask the question whether that reduction of 20 per cent really is going to have an effect on resistance in the future. The continuing legitimate use of antibiotics in humans may still sustain and might even increase the amount of resistance. I also have to say that to reduce the use in humans entirely down to what is legitimate will require an enormous educational effort which will have to be sustained over a long time. The Prescription Pricing Authorities in England and Scotland are now being very open about their data. There are some 270 million defined daily doses written by general practitioner prescription every year in England alone. That is enough antibiotics to treat every man, woman and child in England for five days a year. You can understand the level of selection pressure that is going on in the community. It is extremely difficult to find out any data on the use of antibiotics in hospitals, which in itself is a disgrace. Most knowledge that we have comes from the fact that certain companies collect data for commercial purposes and sell it to marketing companies or parts of pharmaceutical companies, and they do not like this data being used by other people. I did manage to get some data from a pharmaceutical company and I have written out in the text of our evidence exactly how we use that data, but it looks as though there are probably one to two million prescription days of antibiotics in hospital patients, maybe a little bit more, certainly nothing like the order of the 270 million prescription days which are written in general practice. I am rather labouring this point because I think in the past people have talked greatly about what happens in hospitals, standards of infection control, the overuse of antimicrobials and so on, but we have to remember that general practice is extremely important at actually generating a pool of resistant organisms perhaps of certain types, for example penicillin-resistant pneumococci, and maintaining any organisms which go from hospitals into general practice. Also, most prescriptions in general practice are written for oral antibiotics and they have a much greater effect on the

bowel flora than many of the injectable antibiotics used in hospital. When you consider that, for example, faeces contain at least 1,000 million bacteria per gramme of a huge variety of bacteria you can see the sort of selection pressure that you can put on by taking oral antibiotics. As for improving usage in humans, it is quite clear that everybody who prescribes antibiotics of any sort should have an antibacterial formulary, which is a list of preparations that are approved for that establishment or that practice and, much less commonly currently, usage policies. These are policies which tell you what antibiotics to use in particular situations. These cannot be imposed. It is extremely important that the clinicians have ownership of these. It is important they feel comfortable with the formularies and the policies within which they have to work because at the end of the day they are responsible for treating the patients. One of the ways in which you can educate people is to audit the effectiveness of and compliance with formularies and policies because that gets you into dialogue with the people who are actually trying to prescribe antibacterials. I think audit is a very important tool, firstly, in checking that you know that you have done the right thing and, secondly, in education. Unfortunately, at the present time in this country very few hospitals have patient-specific prescribing systems so the only way to do an audit is to go round the hospital and look at each individual patient prescription. That is incredibly labour intensive and not practicable to do on a regular basis. I believe that regular thorough audit of the way that antibacterials are used in hospitals is going to depend very much upon having excellent IT in hospitals, particularly prescribing systems, but hopefully also linked to electronic patient records so you know why the prescription is being made as well as what is being prescribed.

We need much more effort in **medical education**. As I mentioned already, postgraduate education I think should largely depend upon interaction between audit and trying to influence doctors to prescribe directly. That is a relatively easy problem in hospital, apart from the lack of IT. I believe it presents a huge problem in general practice where many practitioners work in fairly isolated circumstances. It is going to be very very difficult to audit what they do and try and influence them, yet for the reasons I gave right at the very beginning I think it is absolutely vital that some thought is given as to how this should be done. In terms of education, I think antibiotics are largely victims of their own success. They are relatively non-toxic agents. It does not matter too much what dose you give. It is very difficult to hurt many people with them, although of course they have tremendous ecological effects. The ill-effects on individual patients are infrequent and because of this people tend to give them casually, and the prescribing of antibacterials is often delegated to the most junior person in the hospital team, usually the houseman. I believe this has got to alter and that doctors have got to take more responsibility right through the whole chain of saying, "Are we really doing the right thing by prescribing antibiotics?" The undergraduate curriculum is extremely crowded and it has been changed very

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heavily recently, as I am sure members of your Committee will know. I believe that there should be a special place for teaching the therapeutics of antimicrobials, not because they are difficult to give but because they are too easy to give yet they have enormous ecological effects.

Lord Porter of Luddenham

46. From your graph it seems to be the case that education is more or less limited to students, postgraduate and undergraduate. Many of the doctors or GPs and so on who are practising now would not have known about the resistance some years ago. Is not education needed beyond the students in universities and so on?

(*Professor Reeves*) I have mentioned postgraduate education. The way to do it by continuing education is to audit people's practice and discuss it with them and that is a form of continuing medical education.

47. Are there facilities for the education of GPs, for example, in these things, and what about the public?

(*Professor Reeves*) Dr Slack has already mentioned about collecting good epidemiological data on resistance. I will just briefly reiterate that it needs to be systematic, linked to populations and to diagnoses, use standard methodologies and definitions, and be evaluated centrally. Again there is a pivotal role for **information technology** here. Many of us who have to report infections centrally at present find it is idiotically labour intensive in that one has it on one's laboratory computer system yet has to take it off the system and write it down again to report it, and all this could be done by superior information technology. I think more investment needs to be made there.

Baroness Masham of Ilton

48. Are some countries better than us at doing this?

(*Professor Reeves*) Not necessarily in collecting good epidemiological data.

Lord Winston

49. Their IT is.

(*Professor Reeves*) IT in North America is better. It might be something you would like to look at because I believe some of you are going there. It is infinitely superior. I met a physician from the Mayo clinic the other day at a meeting and he said, "Oh, you have trouble in auditing your antibiotic use in your hospital. When I go in in the morning all the prescriptions for antibiotics in the hospital have already gone through an algorithm and I am left with about 100 prescriptions which I really feel I ought to have a look at to see whether they are valid." With a system like that you can really get on top of what is going on with antibiotic prescribing in the hospital. We do not have anything like that.

Lord Phillips of Ellesmere

50. Is there evidence that that is helpful?

(*Professor Reeves*) It is very difficult to know whether it has helped the Mayo clinic or not because

it is not a very controlled study. Nevertheless, they do know what is going on.

51. Is this affected by our attitudes to patient confidentiality?

(*Professor Reeves*) I do not think it is to do with patient confidentiality because obviously the medical microbiologist who has a clinical role as well has every reason to need that knowledge. It is a question of a lack of decent IT. We just do not have it in our hospitals.

Lord Phillips of Ellesmere] My Lord Chairman, as you know, this Committee did a study on the uses of IT in modern societies and there seemed to be strong resistance within the medical community to use IT partly for reasons of confidentiality.

Lord Walton of Detchant

52. There would be no problem within hospitals, when exchange of information involves interrelationships between doctors who are involved in the care of the individual patient.

(*Professor Reeves*) I think the BMA's objection was largely about transmitting information between hospitals. They were worried it would go astray.

(*Dr Slack*) Under the Data Protection Act if it is required for public health reasons there is a section where it is allowable to do that and obviously for the direct care of that individual patient then there is no problem. I think the difficulty and where there are problems is in central reporting of that data, but it is quite easy to remove the identifiers of individual patients to collect information on the epidemiology of resistance. What is perhaps more difficult is the audit side which I think has caused some difficulties with individuals.

(*Professor Reeves*) The next thing is about reducing the incidence of infection. Obviously the less infection you have to treat the less antibacterials you are going to use. I will not labour what Dr Hastings said about the hospitals and the poor environmental conditions in hospitals and about controlling infection. In the community that is also important, and we believe that the way to reduce infection in the community is to improve people's health and also to improve their knowledge about avoiding infection. It is of interest that there was a recent study in the United States where people were concerned about catching infection from food yet did not know the most basic rules of kitchen hygiene when questioned about it. I think there is a huge area where the media could help in actually **educating the public** even in quite casual ways. A programme like *Eastenders* will bring up quite interesting medical problems and highlight them in this sort of rather easy to assimilate way and they could easily do the same with, for example, not mixing raw and cooked meat in your kitchen, and so on. It does not cost them anything. There is a huge need for public education. Also, there is a need for reducing public expectation as there is a tremendous pressure on general practitioners to prescribe antibiotics. Patients expect it. We have got to educate the public that this is not always an appropriate form of therapy and there

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[Continued

[Lord Walton of Detchant *Contd*]

are risks both to them and the community. This has got to be got across.

One thing I have not mentioned is the use of **vaccines**. That clearly could be useful, but I am rather gloomy about vaccines preventing many bacterial infections in hospital patients because of the huge variety and the difficulty of making vaccines which would be appropriate. The same may be said to be true of using bacteriophages as well. I think it might be quite difficult to use them in a rational way within hospitals. The **pharmaceutical industry** has been very successful in promoting new antibiotics. There has been a steady increase in the per capita use of antibiotics at least until 1993. It went up by about five per cent per year without any real change in the morbidity of that population and one has to ask why that was going on. Also, the pharmaceutical industry is very good at getting people to shift from old antibiotics to newer and more expensive ones and that again has come out in a number of studies.

I must also mention the **non-human usage of antibacterials**. I think this is an important area which needs to be addressed. Resistance genes which are generated in the animal population are undoubtedly being consumed all the time by humans via the food chain. Clearly the costs of doing something about this are going to be very high.

Lord Porter of Luddenham

53. May I ask you a very quick question about your reference to **bacteriophages**. You said there is a need for a rational use in hospitals.

(*Professor Reeves*) I said it might be difficult to have rational use in hospitals.

54. What use are you contemplating? Is there a use in hospitals?

(*Professor Reeves*) I am not sure. It is again something we should maybe examine in a rather more systematic way—other than in Tblisi! The difficulty is that most bacterial infections are treated empirically and a phage is tremendously specific both to the bacterium and even to the particular strain, and so until you have isolated it you do not know which phage to use. Most patients are treated with an antibacterial agent for two or three days before you isolate the organism.

55. Is there active research outside Tblisi that has been going on?

(*Professor Reeves*) I am not aware of any.

(*Dr Slack*) Dr Soothill, who used to work in our department and in other people's departments here, has been almost single-handedly trying to support this and has been doing some work.

56. You referred to irrational use in hospitals as if there was use in hospitals.

(*Professor Reeves*) No, it would be very difficult to use them rationally in hospitals at present.

57. Is it because of a lack of information?

(*Professor Reeves*) What we know about bacteriophages at the present time is that they are very

very strain specific and that is not the way one treats infections in hospitals generally.

Lord Phillips of Ellesmere

58. My Lord Chairman, Professor Reeves has already said that it would be desirable to identify the infective agent before prescribing an antimicrobial of some kind, so that would fit in with using bacteriophages.

(*Professor Reeves*) That is right, my Lord. The next thing I had in the order of priority was **international co-operation**. I believe that this is a problem which should be raised within Europe to a much higher level.

Lord Gregson

59. Why only in Europe?

(*Professor Reeves*) We need to collect good epidemiological data on a European scale, but Europe has also got to set a good example to the rest of the world before it points a finger at the developing countries, which have the most enormous difficulties because of their lack of infrastructure in health services, in controlling the use of antimicrobials and controlling infection. This is a problem that eventually is going to have to be tackled in the long term on a worldwide scale, but I believe that the order should be the medical profession in Europe puts its house in order, Europe puts its house in order, and then it can ask how it can help the rest of the world. We are setting an example. At present we do not even set them a very good example.

60. Surely the cooperation of people like Japan and America is of equal importance if not more importance.

(*Professor Reeves*) We do co-operate on a scientific level very much indeed, but the real problems, I believe, are the generation of resistance in countries like Africa and the Far East, and with modern travel there is just no way we are going to stop those infections coming in. I do not know if anybody has mentioned to you about penicillin-resistant pneumococci in Iceland. You imagine Iceland as a very clean place and very restrained in its antibiotic prescribing, it is very Scandinavian, and yet in the beginning of the nineties they had an absolute explosive outbreak of penicillin-resistant pneumococci. It went from zero to five or ten per cent over a period of two or three years. Later genetic studies showed that strain almost certainly came from Spain where the resistance is very common. It is a graphic illustration of the way that modern air travel and the desire to find the sun and so on can move organisms around.

Improving the diagnosis of infection so we can better direct therapy from a much earlier stage is absolutely crucial. It is not very fashionable for companies to work on this. Many of the new technologies are quite high cost to develop and ultimately that is going to cost money when they are introduced into the Health Service because new tests tend to cost a great deal

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[Continued

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of money. So it is something we are going to have to recognise.

Finally, **providing new antibacterials** is basically a long-term strategy; it takes so long to bring them to fruition. But there are things that Government can do to help. One is fast-tracking drugs. The Food and Drug Administration (in the USA) has got a fast-track system for important drugs. Another is to provide incentives for "orphan drugs". Orphan drugs are drugs which have very few uses; they are commercially unattractive. Their patent could be extended, for example, to allow the company to get better returns on them. Finally, of course, new antibacterials are always more expensive and there will be costs to the NHS in introducing them into use.

Lord Jenkin of Roding

61. I have a question about **infection control** and the range of measures which might be taken. It is really coming back to Dr Hastings' work in a hospital. What would your reaction be to establishing a control of infection ward so that you have the patients quite separate? You have talked about single rooms but should one not try to group together the infected patients who have been identified, and MRSA is an obvious infection here, as a means of freeing up beds and reducing risks in the other wards?

(*Professor Reeves*) We cohort patients on wards. There are some problems. First of all, it can only be for one sort of infection and if you have got two types of infection then mixing them together is obviously not a good thing on the ward. Secondly, of course, it makes for bed usage inefficiencies because you might have empty beds on the cohort ward and you might actually run yourself short of beds because of that, particularly in the winter, where there is tremendous pressure on medical beds. That could be quite serious. The other difficulty about cohorting is it is quite expensive because it means that only the nurse who is working on that ward can work on it. They cannot go anywhere else. If they have worked on that ward they cannot go anywhere in the hospital because they might be carrying an MRSA they have picked up on the ward. It is so difficult to stop peripatetic people spreading infection. The housemen are peripatetic. They have got patients on wards all over the hospital sometimes. The physiotherapists and all the other people who come and deal with these patients are likely to carry the infection elsewhere unless they are absolutely scrupulous about hygiene. So although it has been used quite successfully in some hospitals at the beginning of the MRSA crisis in London, it is not the total answer.

62. I shall make sure that that reply goes to my Trust!

(*Dr Hastings*) The other problem that we are faced with is increasing specialisation in medicine and to take a patient from one particular unit and put them on an infection control ward is actually very difficult. We have a cardiac transplant unit, a liver transplant unit and a renal unit, and the nursing care is so specialised for those patients that you could not transfer them to

another ward. So it would not work in practice. You need the isolation rooms associated with each unit.

63. You mentioned the question of **antibiotics and animal husbandry**. We have had written evidence to say that the allegation that resistance can transfer from animals to humans has been investigated by experts for decades but has never been proved. What is your reaction to that?

(*Professor Reeves*) My reaction is one of amazement. We know that salmonellas go from animals to humans and many salmonellas carry resistance factors. Professor Wise, for example, has recently written about a gentleman who worked in a chicken factory who got vancomycin-resistant enterococcus which may well have been generated by the antibiotics being used at that time in poultry. I think there is ample evidence that antibiotic resistant organisms spread from animals to humans.

Baroness Platt of Writtle

64. Through the food chain as well?

(*Professor Reeves*) Yes. For every infection that you see there will be a number of subclinical instances of salmonellosis. We all know, for example, with salmonellosis that the clinical attack rate is quite low and if you look at an outbreak you find many people have got the organism in their bowel, and the same will apply to E.coli. It may not affect the person when it comes to them but it may establish itself in their bowel and it may be carrying resistance factors. I do not accept the contention at all.

Lord Perry of Walton

65. You mentioned the fact that 50 per cent of the people in this room would be colonised with Staph. Is there evidence about what proportion of the general public who are colonised will be **colonised with MRSA or VRSA**?

(*Dr Hastings*) I do not know of any national figures for MRSA.

(*Dr Slack*) I think it is still very low, but those that are associated with nursing homes, if you took a specialised population, people who have been in and out of hospital, their rate would be much higher. I think Professor Reeves has got some evidence that new patients coming into hospital who have not recently been in hospital are also MRSA carriers so it must be passing person to person within the community. Overall it is a fairly low proportion at the moment.

Baroness Masham of Ilton

66. Should there be more **screening** when patients come from one hospital to another hospital or from one unit to another unit?

(*Professor Reeves*) We do do that. Firstly, it is incumbent upon the infection control team in the sending hospital to tell the infection control team in the receiving hospital if there is either an infection in the patient or the patient comes from an environment where there is a certain infection and they may be

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[Baroness Masham of Ilton *Contd*]

infected. The receiving hospital can then isolate the patient and screen them and that is what might well happen.

(*Dr Slack*) It might be worth saying that the guidelines on MRSA in hospitals are going to be re-issued possibly later on this year. This is a joint thing between various members of our society, the BSAC, the Hospital Infection Society and the Infection Control Nurses' Association and that does cover

screening of staff and patients transferring between hospitals.

(*Professor Reeves*) With regard to public education, the Association produces a set of "Facts About ..." various infections which I did mention in the text. I will leave a copy with you, if I might. There is nothing about resistance yet!

67. [Unallocated]

68. [Unallocated]

TUESDAY 21 OCTOBER 1997

Present:

Gregson, L.	Rea, L.
Jenkin of Roding, L.	Soulsby of Swaffham Prior, L.
McFarlane of Llandaff, B.	(Chairman)
Masham of Ilton, B.	Walton of Detchant, L.
Perry of Walton, L.	Winston, L.
Platt of Writtle, B.	
Porter of Luddenham, L.	Phillips of Ellesmere, L.

Memorandum by the Public Health Laboratory Service

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2. Tuberculosis
3. Methicillin-resistant *Staphylococcus aureus*
4. Resistance in enterococci
5. Resistance in *Streptococcus pneumoniae*
6. Resistance in gram-negative bacilli
7. Resistance in enteric pathogens
8. Resistance in *Neisseria gonorrhoeae* (gonococcus)
9. *Neisseria meningitidis* (meningococcus)

1. PROLOGUE

Antibiotic resistance is an increasing and serious problem that threatens our ability to treat infections. Antibiotics have been of tremendous benefit in the last 50 years, but some now say we are entering the post-antibiotic era when we will not be able to rely on them. From a scientific point of view, we recognise that the developments of resistance in response to antibiotic use is inevitable.

- (i) Antibiotics are mostly derived from natural microbial products, then modified chemically.
- (ii) They are produced by micro-organisms so there are clearly genes present that produce enzymes that handle these molecules and need minimal change to become antagonists of the antibiotics.

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- (iii) The targets of the antibiotics may change while retaining their physiological function.

The genetic event (mutation) that creates resistance may be a fairly rare event and changes in a target molecule may be much more common than creation of an antibiotic-destroying enzyme—but bacterial population dynamics then take over. Three aspects of this are key to understanding the spread of resistance: size of the bacterial population; rate of replication; capacity for exchange of genetic material—and all of this placed in the context of the selective pressure of antibiotic usage.

- (i) Size of population. There are 10^{14} bacteria per human, so even rare events will be frequent.
- (ii) Bacteria multiply every 15-20 minutes so, under selective pressure, with sensitive organisms killed or inhibited, resistant ones can multiply rapidly to take their place.
- (iii) The whole bacterial world can be considered to have a fluid, interchangeable gene pool, i.e., genetic transfer which is severely constrained to each species in higher organisms through sexual reproduction is far less constrained in prokaryotes; again, although inter-genus transfer of DNA is much less efficient than transfer within a species—a very rare event can occur frequently in the total bacterial world and then be selected.

There is also the fact that many resistance genes have become packaged in sets, so that use of one antibiotic creates the selective pressure for a whole set of resistances, i.e., for multi-resistant strains.

So, selective pressures are the key to antibiotic resistance which means that the amount of antibiotic put into the environment of the bacteria (our human bodies, animals, the outside environment) determines the selective pressure for resistance.

- (i) The development of new antibiotics—no new class of antibiotic has come on the market for 20 years (quinolones were the last—everything since then has been a modification). There is little prospect of new agents in the immediate future.
- (ii) Vaccines—these are expensive and difficult to produce, but can help in some specific cases (e.g. pneumococcal infection) but not in the widespread context.

So, there is an imperative to conserve what we have through:

- (iii) Protocols, guidelines, policies for use of antibiotics to reduce the selective pressure.
- (iv) Control of infection measures to stop the transmission of resistant strains. This cannot be over-emphasised.

If an attempt is to be made to control or limit the spread of resistance, data are needed on the incidence and trends in resistance—this is the purpose of surveillance, which is defined as information for action. In order to plan action, we need to know the scale of the problem, and we need to have a measure of what happens following any intervention such as prescribing protocols and restrictions on use.

PHLS is responsible for the surveillance of communicable diseases in England and Wales. The focus for surveillance is the Communicable Disease Surveillance Centre (CDSC) with specific organism data from the reference laboratories at the Central Public Health Laboratory (CPHL), supported by the network of PHLs. Data are collected from PHLs and NHS laboratories around the country.

Most surveillance data collected by CDSC are related to specific organisms or diseases, with antimicrobial susceptibility data collected as an adjunct to disease surveillance. Other specific programmes of antimicrobial susceptibility surveillance are aimed specifically at continuous or intermittent monitoring of particular resistance problems. For some routine antibiotic susceptibility surveillance, the PHLS depends upon information reported to it voluntarily and the data generally lack denominator information and may be skewed by the reporting of more interesting (more resistant) isolates. For specific areas of concern, reference laboratories collate data on resistance e.g., enteric bacteria, tuberculosis.

The following sections on specific aspects of antimicrobial resistance have been provided by PHLS staff in the Central Public Health Laboratory (CPHL) and other Reference Units and in CDSC.

2. TUBERCULOSIS

2.1 Background

Tuberculosis (TB) remains numerically the most significant single infectious cause of morbidity and mortality producing nearly 8 million cases worldwide and 3 million deaths annually and causing approximately one-quarter of all avoidable adult deaths from infection in the developing world. The steady decline in clinical tuberculosis cases seen in the developed world, and some parts of the developing world, ceased or reversed in the mid-1980s.

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There are several possible explanations for the increase in cases of active TB world-wide but inevitably the causes in any geographical area will be multifactorial including:

- (a) co-infection with the human immunodeficiency virus (HIV), arguably the single most important risk;
- (b) failure to give priority to national TB control programmes and/or poorly organised programmes with poor case finding, treatment rates and compliance;
- (c) reduction or withdrawal of donor agency support to international TB control programmes;
- (d) increasing numbers of homeless or displaced people sheltering in crowded conditions and overcrowding in institutions such as prisons and hostels;
- (e) intravenous drug abuse;
- (f) immunocompromised status due to extremes of age, alcoholism, diabetes mellitus, renal failure;
- (g) increased immigration from countries of higher prevalence.

2.2 *Mycobacteriology services in the UK*

In England and Wales, mycobacterial cultures isolated by National Health Service (NHS) and Public Health Laboratory Services (PHLS) laboratories are referred on a geographical basis to one of four PHLS Regional Centres for Mycobacteriology (RCM), co-ordinated by the PHLS Mycobacterium Reference Unit (MRU) which acts as the Regional Centre for southern England. Over 95 per cent of mycobacterial cultures are referred to these four centres and to the Scottish MRU. Identification is performed using a variety of methods including microscopy, growth characteristics, biochemical tests, molecular hybridisation systems and other specialised systems.

Drug susceptibility testing is performed in solid or liquid media by standardised methodology including the resistance ratio, MIC and proportion methods. Mycobacterial identification and drug susceptibility methods are rigorously quality controlled to form an integrated mycobacterial reference network. All RCMs receive primary specimens from local hospitals and from other institutions in their region and the PHLS MRU offers a national service of specialised molecular investigations for diagnosis and drug susceptibility testing, and molecular epidemiological typing including the investigation of outbreaks and the surveillance of drug resistance. The mycobacteriology reference network with the PHLS Communicable Disease Surveillance Centre (CDSC) forms an integrated tuberculosis programme to provide diagnostic, reference, epidemiological, clinical and research activities at local, regional and national levels.

2.3 *Treatment of tuberculosis*

Unusually among bacterial infections, *Mycobacterium tuberculosis* infection is treated with a combination of three to four agents for prolonged periods of at least six months duration. Monotherapy rapidly leads to the development of drug resistance by selecting for spontaneously occurring resistant isolates in the population of bacteria infecting an individual.

Drug resistance emerges when there is non-adherence to combination drug chemotherapy due to poor compliance on the part of the patient, incorrect prescribing on the part of the physician or some physiological problem such as malabsorption due to gut infection by other bacteria, virus or parasites as is commonly seen in immunocompromised patients. Certain drugs such as antacids may prevent the absorption of anti-tuberculosis drugs.

Arguably the greatest treatment problem relates to those individuals infected with multiple drug resistant TB isolates defined as those bacteria resistant to the drugs isoniazid and rifampicin. Mortality is high and in a landmark study in HIV negative patients the overall mortality rate with individualised treatment was 44 per cent. The mortality rate in HIV positive patients can be as high as 80-90 per cent. Recent studies in New York have demonstrated a significantly improved outcome with survival rates of 50-60 per cent. These studies showed that response and survival were positively affected by the administration of more than two drugs to which the isolate was susceptible on rapid *in vitro* testing. Rapid diagnosis of drug resistance, therefore, has a proven benefit in clinical outcome and arguably a benefit to public health as these patients were rendered smear negative (i.e., non-infectious) much earlier than would have been the case otherwise.

Unfortunately there is also recent evidence that long-term survival in HIV positive patients where there is a delay in diagnosis or an undiagnosed epidemic remains bleak: in a nosocomial outbreak spanning almost four years that occurred in an HIV ward at a Madrid infectious disease hospital, 47/48 (98 per cent) of cases died with a mean interval from diagnosis to death of 78 days.

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2.4 Tuberculosis and drug resistance

Resistance to anti-tuberculosis drugs was recognised to be a problem shortly after the introduction of the first effective agents in the 1940s. The use of three or more drugs in combination (multi-drug therapy) is generally effective in preventing the emergence of drug resistance, but resistance has continued to occur, particularly in areas where the application of treatment regimens has been less than optimal. As tuberculosis re-emerged as a major global health problem at the end of the 1980s and early 1990s, fuelled by global population increase, urbanisation and the HIV pandemic, drug resistance has also become an increasing problem.

Reliable data are not available on levels of anti-tuberculosis drug-resistance from most parts of the world but those surveys that have been carried out suggest that in some areas rates of drug resistance to first-line anti-tuberculosis drugs are very high. In some parts of the developing world multi-drug resistance, i.e., resistance to rifampicin and isoniazid (with or without resistance to other drugs) is especially high.

A national survey of drug resistance in the United States has just been published (reference 1). The survey covered the years 1993–96 and gave estimates of the levels of drug resistance in initial isolates (i.e., isolates of *M.tuberculosis* obtained at the time of diagnosis of a new patient with tuberculosis). Overall resistance to isoniazid (with or without resistance to other drugs) was 8.4 per cent and multi-drug resistance was 2.2 per cent. In comparison with the previous surveys in the United States in 1991 and 1992, isoniazid resistance has remained relatively stable and multi-drug resistance has decreased a little.

2.5 Drug resistance in England and Wales

A review was carried out on drug resistance in initial isolates of *M.tuberculosis* submitted to the PHLS Mycobacterium Reference Unit or Regional Tuberculosis Centres in residents of England and Wales between 1982 and 1991 (reference 2). Overall 6.1 per cent of the initial isolates were reported to be resistant to isoniazid (with or without resistance to other drugs) and 0.6 per cent of isolates were multi-drug resistant. No trend to increase was observed during this 10 year period. However in the light of the resurgence of anti-tuberculosis drug resistance as a major problem worldwide, the PHLS decided to establish a continuous surveillance system for drug susceptibility on all isolates of *M.tuberculosis* in England and Wales co-ordinated by the Communicable Disease Surveillance Centre, in collaboration with the Regional Centres and Mycobacterium Reference Unit. As a result of the enthusiastic collaboration of colleagues in Scotland and Northern Ireland, the surveillance system, called the UK Mycobacterial Resistance Network or MYCOBNET, collects data for the UK as a whole. Isoniazid resistance (with or without resistance to other drugs) in the UK in 1993, 1994 and 1995 was 4.6 per cent, 5.4 per cent and 5.5 per cent respectively. Multi-drug resistance rose from 0.6 per cent in 1993 to 1.2 per cent in 1994 and 1.2 per cent in 1995.

2.6 Future developments

Levels of resistance to anti-tuberculosis drugs in England and Wales remain relatively low but the recent increase in multi-drug resistance is of some concern. These data relate to resistance in isolates obtained from patients at the time of diagnosis and do not include cases of drug resistance occurring in patients who develop drug resistance whilst on treatment. In order to prevent the development of drug resistance in patients with tuberculosis, it is essential that appropriate drug therapy should not only be commenced but also completed. In some patients this may require the full supervision of therapy, so called "directly observed therapy". Robust and well-organised services for the management of patients with tuberculosis are essential for all cases in England Wales and are particularly important in those health authorities seeing many cases. The Department of Health has recently issued guidance of these services and these recommendations should be adopted by all health authorities (reference 3).

The laboratory is essential to support the diagnosis of tuberculosis, identify the occurrence of drug resistance and monitor the subsequent process in drug resistant cases. Conventional methods to identify *M.tuberculosis* from clinical specimens, and to determine drug susceptibility of the isolates, take 3-6 weeks or longer. Rapid methods, based on molecular techniques, are being developed and provide the potential of a considerable improvement in the ability to identify and manage tuberculosis cases, particularly those with drug resistant disease.

Surveillance for drug resistance to anti-tuberculosis medications is essential and the continuation of the current PHLS MYCOBNET Scheme is a high priority. Proposals for the development of other aspects of tuberculosis surveillance will make it possible to link the identification of cases of tuberculosis with their drug sensitivity pattern and their subsequent outcome following treatment. Support for the development of this surveillance is essential.

The PHLS is actively participating in World Health Organisation and European Union collaborative schemes for collating and standardising information on the occurrence of drug resistance in tuberculosis in countries all around the world. These collaborations provide the potential for countries to compare their levels of drug

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resistance with other countries and learn from the experience of others involved in controlling this problem. The PHLS is not only contributing data to these collaborative projects but is also involved in the development of the epidemiological surveillance methods and the microbiological support.

2.7 International surveillance of drug resistance

A recent review of 63 drug resistance surveys performed between 1985 and 1994 indicated that the rates of primary resistance ranged from 0 to 16.9 per cent (median 4.1 per cent) for isoniazid, from 0 to 3 per cent (median 0.2 per cent) for rifampicin, from 0 to 4.2 per cent for ethambutol and from 0.1 to 23.5 per cent (median 3.5 per cent) for streptomycin. As expected rates of acquired resistance were higher with median rates of resistance of 10.6 per cent for isoniazid, 2.4 per cent for rifampicin, 1.8 per cent for ethambutol and 4.9 per cent for streptomycin. The incidence of primary MDRTB ranged from 0 to 10.8 per cent (median range 0.5 per cent) but for acquired resistance the rate varied from 0 to 48 per cent (median rate, 12.2 per cent). Ideally a country-wide survey in which drug susceptibility testing is performed on isolates from all culture positive cases would be preferable. Such studies are costly and resource intensive and so uncommon.

The WHO/IUATLD Global Surveillance Project (GSP).

From the above it is clear that knowledge of current drug resistance rates is essential for the planning of individual treatment, to develop national therapeutic regimens and to assess the current effectiveness of TB control programmes.

The objectives of the GSP are to collect comparable global drug resistance data based on the development of national surveillance programmes under the guidance of a network of supranational reference laboratories (SRL) performing drug susceptibility testing using accepted standardised methods. Drug susceptibility data obtained by the national laboratory are verified by a quality control system based on the SRL network. The PHLS MRU is one of these laboratories and has recently been designated a WHO European Co-ordinating Centre.

A national co-ordinator in each country is responsible for the inclusion of a representative sample of culture derived from new sputum smear positive cases and collating the data needed to distinguish initial and acquired drug resistance. Sputum samples are decontaminated, cultured on Lowenstein-Jensen media and the resulting cultures identified using standard methods. Drug susceptibility testing is performed using the proportion, resistance ratio, or absolute-concentration methods. Data are analysed using standard software developed by the WHO. Data representing 40 countries have been collated so far including data from national programmes associated with SRLs and will be published shortly.

REFERENCES

1. Moore M, Onorato I M, McCray E, Castro K G. Trends in drug-resistant Tuberculosis in the United States, 1993–1996. *JAMA* 1997;278(10):833-7. Communicable Disease Report 1993;3:R175-179.
2. Warburton A R E, Jenkins P A, Waight P A, Watson J M. Drug resistance in initial isolates of *Mycobacterium tuberculosis* in England and Wales, 1981–91. Communicable Disease Report 1993;3:R175-179.
3. The Interdepartmental Working Group on Tuberculosis. The Prevention and Control of Tuberculosis in the United Kingdom: Recommendations for the Prevention and Control of Tuberculosis at local level. Department of Health and Welsh Office, 1996.

3. METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

3.1 Background

Much data on MRSA have already been presented to the committee in the following documents:

- Results of the 1995 PHLS Laboratory for Hospital Infection (LHI) ICT questionnaire MRSA survey.
- World Health Scientific Working Group Report on the Global control of MRSA; WHO, Geneva, Switzerland, 1995.
- The Report of the World Health Scientific Working Group on monitoring and management of bacterial resistance to antimicrobial agents. WHO, Geneva, Switzerland, 1995.
- The clinical audit project has been submitted to the committee. This has chapters on antibiotic prescribing policies and audit and there is an interesting section on the induction process for clinical staff in the Appendix.

Some general points are as follows:

- The induction process for new staff members is often deficient with little time for discussion. The policies are not even given to staff at this session in some of the hospitals.

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- Antibiotic prescribing audit and teaching are irregular and often infrequent. Some sort of audit is performed by microbiologists and pharmacists but this needs to be more structured.

The name of an antibiotic document does not reflect its content. A Formulary can in fact be a text book on all aspects of antibiotics. The documents vary in many parameters as seen in the Tables in Chapter 10 and are drawn up with little involvement of the junior staff; comments are often not invited.

In particular documents varied in size and content, in the number and the way in which antibiotics were listed, or whether they cross-referred to the British National Formulary (available to all doctors). They also varied in whether there was a policy for:

Urinary tract infections: e.g., catheterised patients (13 of the 19), preventative (4). Pneumonia: Post operative (3), Ventilators (1), Aspiration (7). Central venous line infections (5).

- There were many well described processes in place in the audit hospitals but they varied greatly as follows:

The consultant microbiologist (CMM) has to be contacted for certain agents to be prescribed (68 per cent).

Pharmacist informed CMM for certain agents (68 per cent).

Consultant's or registrar's signature required for certain agents (21 per cent).

Automatic stops on prescribing (31 per cent).

3.2 Levels of resistance in UK and abroad

Surveillance methods vary in different countries but several prevalence and other surveys have been performed and show a recurrent theme of frequent variation in different wards in the same hospital, hospitals in the same city, between cities and certainly countries. Holland and Denmark have amongst the lowest incidence of MRSA due to their effective antibiotic and infection control policies. Southern, and Eastern Europe would appear to have higher levels and Northern European countries are fast catching up. There are several data in the above material from the WHO.

In the UK the description of epidemic strains (EMRSA) by LHI has led the way for other countries to also analyse their own EMRSA (e.g., Belgium, Spain, Portugal, Germany). In this decade EMRSA-15 and 16 are affecting many regions as shown in the CDR reports (see Appendix). Virulence is apparent from the prevalence of surgical infections in the second National Survey (. . . 20 per cent of *S.aureus* wounds) and the bacteraemia reporting system of CDSC/LHI.¹ In the last six years the rate of MRSA bacteraemia has increased . . . six fold to 13.7 per cent of all *S. aureus* bacteraemias and is probably nearer 20 per cent this year.

Some of the best data are from the recent infection control team questionnaire, this shows huge variations in the amount of sepsis, septicaemias and MRSA isolates around the country. The reasons for this reflect on the variation between the type of MRSA, the type of patients and many aspects of health care delivery.

We are fortunate at present in that the current MRSA in the UK are more susceptible to antibiotics than in some other parts of the world. Most can be treated with fusidic acid, rifampicin, trimethoprim and even tetracycline and gentamicin. Antibiotics are often used in combinations to treat severe MRSA infections.²

Mupirocin resistance is emerging and is causing problems in some hospitals where resistance is at a high level. Low level vancomycin resistance in MRSA has been described in Japan and perhaps the USA. It is treatable with several other antibiotics some of them in combination with vancomycin. However, genuine resistance has yet to be encountered and the vancomycin resistance genes of the enterococci have not been seen *in vivo* in staphylococci, although this appears to be possible in the laboratory.

3.3 Measures to reduce or at least stop the rise of resistance

The measures to control MRSA are outlined in the 1990 MRSA control guidelines and are endorsed by the DH. A new working party has completed the revision of these guidelines and the professions are considering them at present. Agreement is difficult as there are so many different experiences. An overview of the new guidelines can be provided if the Committee wishes, outlining the more contentious areas. The previous guidelines apply if there is not an endemic situation; the definition of endemic has to be agreed. Where it is endemic then a risk assessment approach is suggested. ICTs should agree a grading of their susceptible units into high, medium, low and minimal risk. The types of screening vary according to the risk and an isolation strategy is also advocated. Briefly, a part of a ward may be used to contain MRSA rather than have many patients scattered throughout the hospital. If numbers of MRSA patients are large or disruption of services significant, then a whole ward may be justified.

Many of the control measures advocated are outlined in the ICT questionnaire and will not be repeated here.

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There is the interesting area of antibiotic prescribing control. There are many studies describing the effects of antibiotic prescribing on MRSA, but few control for length of stay which also increases the chances of acquisition. Increasing antibiotic resistance within MRSA, e.g., to quinolones, mupirocin, are also obfuscated by this problem. Once methicillin and some of these other resistances has emerged it can be very stable (particularly if due to gene mutation) and may not be influenced by antibiotic prescribing control measures. Despite these problems most infection control professionals advocate an antibiotic prescribing control policy. There would appear to be more evidence for its success in the community, for vancomycin-resistant enterococci (VRE) and other antibiotic resistance organisms.

3.4 Monitor the problem and inform control measures

Surveillance of MRSA needs to be improved; we would like to introduce the voluntary reporting system we had in the 1980s. Since that time we are referred MRSA from most of the country and the ICT questionnaire would suggest that we have a fairly accurate picture of the spread of strains and size of the problem. The surveillance information is integral to the advice we give to infection control teams on a regular basis (two to six enquiries per day). We are about to introduce a new reporting form for our isolates which will further improve the information which we can provide to our customers (on an aggregated confidential basis). The introduction to LHI of a computer database will also improve matters and this will be harmonised with any other reporting systems for maximum benefit.

3.5 New antibiotics

The struggle to discover new antibiotics is well known and can be reduced to one section of this report. MRSA are, on the whole, more virulent than VRE. Stopping antibiotics and removing indwelling devices such as urinary catheters and central lines is often sufficient in VRE but not so for MRSA. VRE are often mixed with other (more genuine) pathogens, unlike MRSA.

3.6 Research

There is a huge amount of work required in this area including clinical studies. The new guidelines outline the areas where knowledge is required and are a good starting point. Several studies are underway and other grant applications are being progressed.

REFERENCES

1. Cookson B D. Is it time to stop searching for MRSA? *Br Med J* 1997; 31: 664-666.
2. Cookson B D. Treating MRSA bacteraemia. *Med Microbiologist* 1997;1:5.

4. RESISTANCE IN ENTEROCOCCI

4.1 Introduction

Enterococci form a part of the normal human gut flora. They have low virulence, but can cause infections in patients whose resistance to infection is impaired. Enterococci are therefore a risk mainly to patients in hospital units such as renal dialysis and bone marrow transplant units. If they gain access to normally-sterile body sites in vulnerable patients, they can cause many types of infection, from superficial infection of skin wounds and urinary tract infections to serious infections, including septicaemia and endocarditis. Serious infections are extremely difficult to treat because of the degree of antimicrobial resistance.

4.2 Resistance to Antimicrobials

Enterococci are intrinsically (naturally) resistant to a wide range of antimicrobials. They are resistant to all available cephalosporins and the use of these agents in specialised hospital units frequently gives enterococci a selective advantage and has been cited widely as a major reason for the rising clinical importance of enterococci. Enterococci are relatively-resistant to quinolones and penicillins (and are usually tolerant to the bactericidal action of the latter), and are insusceptible to aminoglycosides.

In addition to their intrinsic resistance, enterococci readily gain resistance to other antibiotic classes, usually by acquisition of resistance genes as parts of transferable plasmids or transposons, either from other enterococci or from other (usually undefined) bacterial species. Thus enterococci currently isolated from hospital patients are resistant to many agents, including tetracyclines, macrolides, chloramphenicol, trimethoprim. Furthermore,

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high-level penicillin resistance (resulting from chromosomal mutations) and high-level aminoglycoside resistance (resulting from transferable plasmids) are increasingly encountered, frequently in combination with each other and the other resistances listed above. As with staphylococci, for many years, glycopeptides (vancomycin and teicoplanin) were the only agents to which enterococci could be assumed to be sensitive with any degree of confidence. But resistance to these agents, which represent the "last line" of defence against severe Gram-positive infection, emerged in the UK in 1986 and has subsequently spread to many hospitals (see below). Many glycopeptide-resistant enterococci (GRE), particularly *Enterococcus faecium*, are resistant to all established antibiotics, forcing clinicians to use less-favoured options, or new, relatively-untested agents, often with no guarantee of a successful outcome.

4.3 A Spectre for the Future

Many types of antibiotic resistance are common to enterococci and staphylococci. Two distinct forms of transferable glycopeptide resistance occur in enterococci, called VanA and VanB. The VanA form exists in many countries and the potential for its transfer to more pathogenic species, such as *Staphylococcus aureus*, has caused great concern. Such transfer has been demonstrated in the laboratory, but to date, clinical recognition of *S. aureus* with enterococcal glycopeptide resistance genes has not been documented. The public health and economic consequences of the emergence of high-level glycopeptide resistance in methicillin-resistant *S. aureus* (MRSA) would be catastrophic. Hence, a detailed understanding of glycopeptide resistance in enterococci will inform opinion regarding the possibility of such spread.

4.4 The UK Situation in Comparison with other Countries

No central data on the number of cases of infection with GRE (or other resistant enterococci) are collected. However, national epidemiological data are compiled by the Public Health Laboratory Service, from isolates (specimens of bacteria isolated from patients) submitted voluntarily by hospitals in England and Wales for specialist microbiological tests. From 1987 to August 1996 the PHLS Laboratory of Hospital Infection (LHI) received GRE (VanA or VanB) isolated from over 1,100 individual patients in 93 UK hospitals (Figure 1). Eighty-eight per cent of isolates had the VanA resistance type (Figure 2) and the distribution of affected hospitals throughout the UK (Figure 3) suggests that GRE emerged independently at a number of different centres, rather than spreading between centres. An alternative explanation for the hospital distribution is that GRE spread to all of them following spread in the community via foodstuffs (see section 4 below).

The hospitals affected range from large teaching hospitals to district general hospitals and, although the majority have referred only sporadic isolates, outbreaks have been investigated at 25 hospitals. The foci of these outbreaks were on specialised units, such as the renal, haematological, intensive care and liver units, but strains have also spread to other units. In several hospitals multi-resistant GRE have become an endemic problem. The epidemiology of nosocomial GRE involves both the spread of strains between patients and the spread of glycopeptide resistance genes between strains. In LHI, we have proposed five epidemic glycopeptide-resistant strains of *E. faecium* (EVREM), of which EVREM-3 is causing greatest concern; it is usually multi-resistant, can spread rapidly within a unit and has been isolated in 16 hospitals.

As with the UK, few other countries have published national figures for numbers of GRE infections. In a recent article on the global impact of GRE (Curr. Opin. Infect. Dis 1997;10:304-9), McDonald & Jarvis noted that the bacteria were reported in an increasing number of countries and that, during 1996, GRE were reported for the first time from Sweden and Australia, while the first hospital outbreaks had occurred in Germany, Italy and Canada. These authors noted that in the US, "the percentage of states with a National Nosocomial Infections Surveillance system hospital reporting more than one [GRE] increased from eight out of 30 (27 per cent) in 1989-93 to 16 out of 36 (44 per cent) in 1994-95." Furthermore, "among nosocomial enterococci causing infection in surveillance system hospitals, the percentage resistant to vancomycin increased in intensive care unit patients from 0.4 per cent in 1989 to 10.8 per cent in 1995, whereas the percentage from non-intensive care unit patients increased from 0.3 per cent in 1989 to 10.4 per cent in 1995."

4.5 The Origins of GRE

It was thought for some years that GRE originated in hospitals as a result of the extensive clinical use of glycopeptides. However, there is now considerable evidence in Europe, to suggest that this is not altogether true. GRE may be ubiquitous in community, sewage and animal sources and may spread to humans via the food chain. The first publication to provide supportive evidence for this was from Oxford PHL; GRE were isolated from farm animals and from raw meat purchased from retail outlets in the UK. Several studies have implicated the use in Europe (including the UK) of avoparcin (a glycopeptide used as a growth promoter in the poultry and pig-rearing industries) as a selective pressure. The EU SCAN (Scientific Committee for Animal Nutrition) committee investigated the proposed link between avoparcin and GRE, but decided that there was a lack of conclusive scientific evidence. Despite their recommendation for further research, the use of this agent as a feed

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additive has been suspended. The presence of GRE in raw meat has been confirmed in by several other European groups. All of these enterococci have had the VanA resistance type. In the prototype VanA enterococcus (isolated from a French hospital patient in 1987), the resistance genes are located on a transposon designated Tn1546. The VanA enterococci isolated from meat in the UK during the period 1993–96 (and in Europe) contain elements indistinguishable from, or highly related to, this transposon, suggesting widespread dissemination has occurred.

4.6 Combating Antibiotic-Resistant Enterococci

4.6.1 Development of new antibiotics

Clinically, the major problem associated with multi-resistant enterococci is the lack of antibiotics with guaranteed bactericidal activity. Several new agents are in development, but many (e.g., the glycyclines) are only bacteriostatic. A semi-synthetic vancomycin-derivative, LY333328, has shown promising *in vitro* activity (and, surprisingly, is bactericidal against many GRE), but may not be developed because of toxicity problems. There has been considerable interest in the injectable streptogramin combination quinupristin/dalfopristin (Synercid™), which may be licensed for use in the near future and which shows good bacteriostatic activity against many multiresistant strains of *E. faecium*. However, resistance may spread fairly rapidly after the introduction of this agent into clinical use. The PHLS Antibiotic Reference Unit has already noted transferable resistance to Synercid™ in glycopeptide-resistant *E. faecium* isolated from raw chicken and hospital patients. There have been similar observations of resistance in Germany and Denmark and it seems likely that use of a related agent, virginiamycin, as an animal feed additive may already have selected a reservoir of resistance genes.

4.6.2 Rational use of antibiotics

The situation with enterococci is comparable with arguments for other bacteria. The use of avoparcin and virginiamycin as feed additives, with the associated risks for selecting truly multi-resistant enterococci requires the issue of non-clinical use of antibiotics to be addressed again.

4.6.3 Understanding the epidemiology of resistance

Many aspects of the epidemiology of GRE still remain unanswered and must be understood if we are to develop rational approaches towards their control.

1. The relative importance of the clinical use of vancomycin and teicoplanin vs. the use of avoparcin for animal growth promotion as factors promoting the evolution, selection and dissemination of glycopeptide resistance requires extensive further study.
 - Molecular typing studies are necessary to determine the degree of relatedness shown by strains of VanA GRE from human and non-human sources. These studies will establish whether exchange of strains occurs or whether some strains are specific either to humans or to animals.
 - Characterisation of resistance elements from VanA enterococci of human and non-human origin will indicate the extent to which exchange of resistance genes may have occurred between these populations.
 - The reservoir of VanA resistance genes will continue to exist in animal enterococci, despite the suspension of avoparcin use. Will replacement ergotropic agents continue to select for this? If resistance to these other agents is carried on the same plasmids that carry the glycopeptide resistance genes, then the latter will persist in the population. If resistance genes are present in animals, there is the potential for transmission of those genes to enterococci in humans.
 - Studies of the ability of animal isolates of VanA enterococci to transfer resistance to enterococci isolated from humans will indicate the possible risk this reservoir poses to human health.
2. How widespread are GRE in raw meat and meat products within the UK?
3. The presence of VanB enterococci in sources outside of the hospital environment remains to be proven. Their apparent absence is puzzling, but could indicate major differences in the epidemiologies of the VanA and VanB resistance types. The existence of an environmental reservoir of enterococci with the VanA resistance genes, but no similar reservoir of enterococci with the VanB genes could also contribute significantly to the different isolation rates (Figure 2).
4. How widespread are GRE in the community population within the UK? Are the strains found in food are also present in the community and are the strains found in the community the same as those currently causing problems in UK hospitals?

Figure 4.1

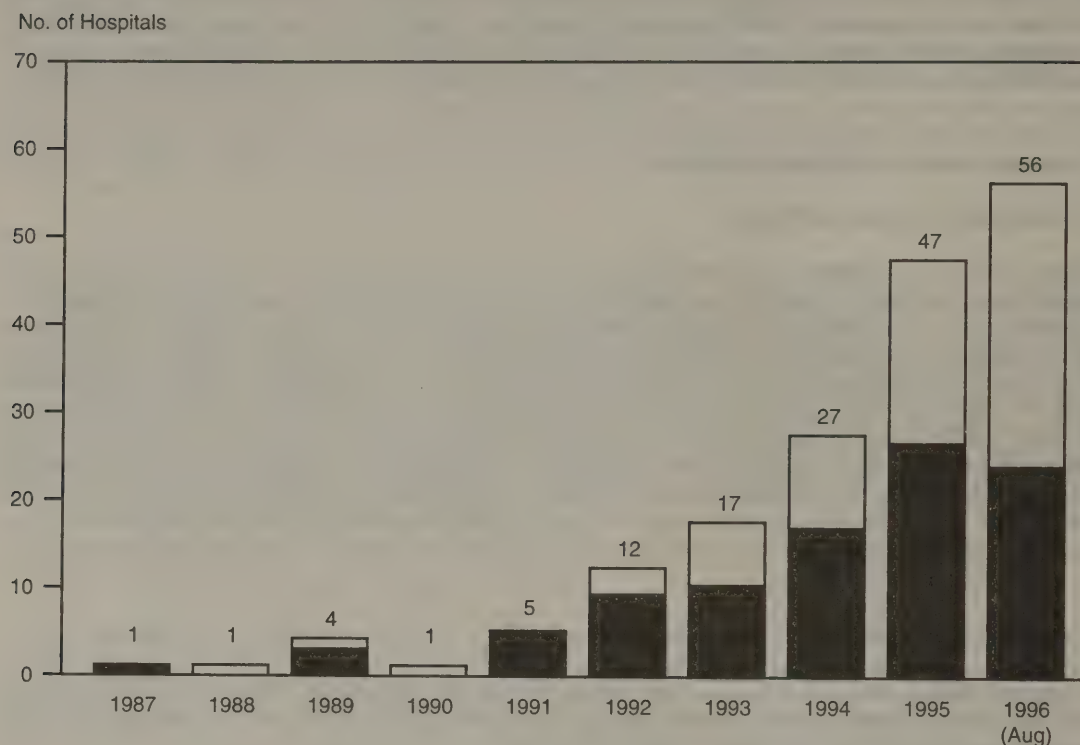


Figure Legends

Figure 4.1. Numbers of UK hospitals referring GRE to the PHLS Laboratory of Hospital Infection between 1987 and August 1996. ■ indicates hospitals referring for the first time. □ indicates hospitals that had referred in previous years. The total number of referring hospitals in each year is shown at the top of each column. Over the period shown, the cumulative total of affected hospitals was 93.

Figure 4.2. Species and resistance types of GRE referred to the PHLS Laboratory of Hospital Infection between 1987 and August 1996. A total of 1120 isolates were received from individual patients at 93 hospitals. ■ indicates VanA resistance. □ indicates VanB resistance.

Figure 4.3. Distribution of 93 hospitals referring GRE to the PHLS Laboratory of Hospital Infection between 1987 and August 1996. ● indicates VanA GRE, ○ indicates VanB GRE and ○ indicates hospitals referring both types.

Figure 4.4. Distribution of hospitals from which the five strains of epidemic vancomycin-resistant *Enterococcus faecium* (EVREM) have been isolated. Inset shows hospitals in the London area.

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[Continued

% of
Isolates
(n = 1120)

Figure 4.2

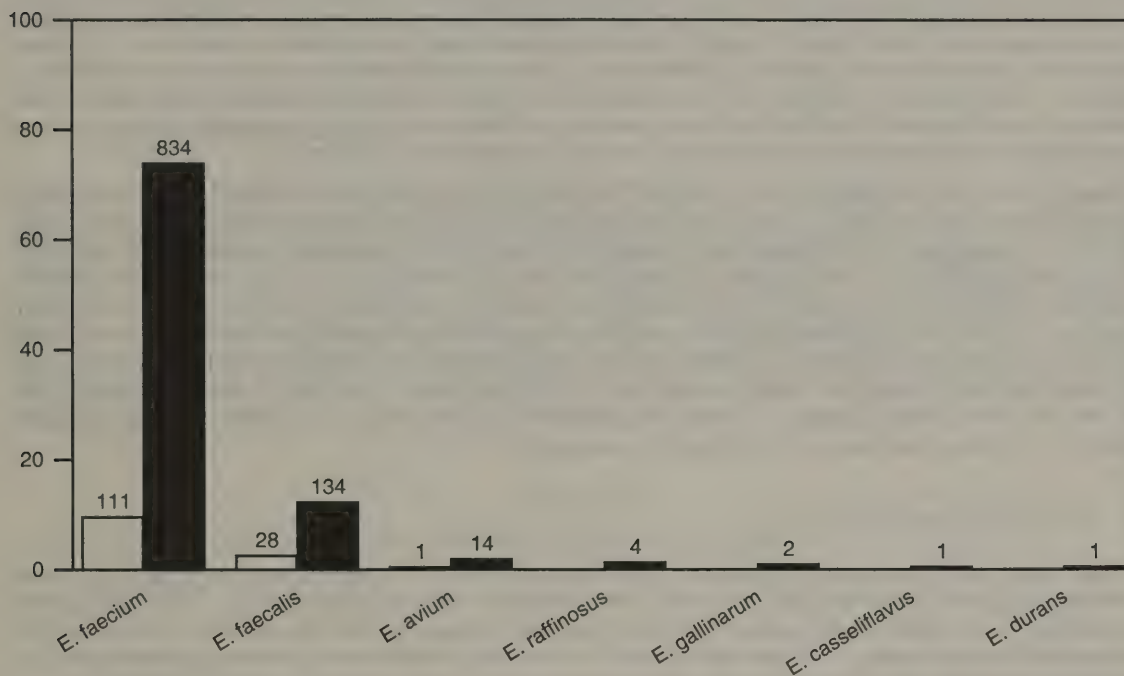
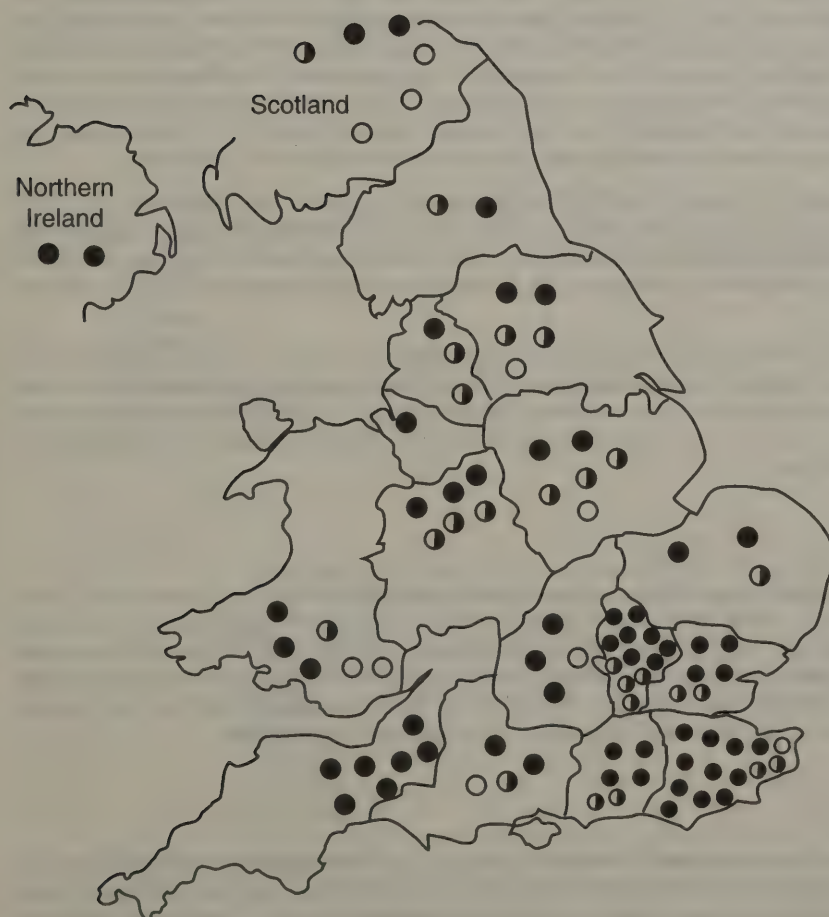


Figure 4.3



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5. ANTIBIOTIC RESISTANCE IN *Streptococcus pneumoniae* in the UK

5.1 Introduction

S. pneumoniae is most important as a cause of pneumonia which may lead also to bacteraemia. In addition, *S. pneumoniae* is a frequent cause of middle ear infection, particularly among children, and is one of the two commonest causes of bacterial meningitis. Historically, *S. pneumoniae* isolates were exquisitely susceptible to penicillin, which could be used in most pneumococcal infections including—critically—meningitis, where delivery of adequate levels is difficult with many antibiotics. Macrolides (e.g., erythromycin), tetracyclines and co-trimoxazole were alternatives in RTI, whereas several cephalosporins are alternatives in meningitis.

Strains with low level penicillin resistance (MIC, 0.12-1 mg/l, compared to ≤ 0.03 for fully sensitive isolates) were recorded in the late 1960s and those with higher-level resistance (MIC ≥ 2 mg/l) began to be seen in the late 1970s. Subsequently, as discussed below, penicillin resistance has disseminated internationally and many penicillin-resistant isolates have acquired resistance to alternative therapies. The significance of penicillin resistance varies with its level and the site of infection. Strains with low-level, still respond to penicillin in respiratory tract infection and bacteraemia, but not in meningitis where, however, cephalosporins can be used. Strains with “high level” penicillin resistance may still respond to high-dose penicillin in the respiratory tract but—with MICs of 8 mg/l now being recorded for some isolates there is little doubt that the “border of the possible” has been reached. Strains with high level resistance are often barely susceptible to cephalosporins in meningitis, and these may need combination with vancomycin.

5.2 PHLS surveillance activities

Since 1989, increasing numbers of isolates of *S. pneumoniae* resistant to penicillin and/or penicillin or other antibiotics have been submitted each year to the PHLS Antibiotic Reference Unit (ARU). There has also been an increase in the number of hospitals submitting isolates, suggesting that the problem of resistance in pneumococci was spreading. Although this indicates an increasing trend towards resistance, the tendency of hospitals to preferentially refer resistant pneumococci precludes assessment of a national prevalence rate for resistance.

For this reason, other surveillance activities have been undertaken by the ARU. In one investigation, all pneumococci isolated (irrespective of site of isolation and resistance pattern) were sent to the ARU for susceptibility testing during a two week period in March 1990 from each of the 52 Public Health Laboratories in England and Wales. The objective was to obtain a “snapshot” of the prevalence of resistance at that time. Exactly five years later in March 1995, the investigation was repeated. Analysis showed that rates of resistance to both penicillin and erythromycin had increased over the five-year period (Table 5.1). It was reassuring, however, that resistance to rifampicin and vancomycin was not detected in either survey (Table 5.1).

Increasing prevalence of resistance to penicillin and erythromycin was also noted when reviewing the results of susceptibility tests for pneumococci isolated from blood culture or CSF in hospitals throughout England and Wales. Penicillin resistance increased gradually but consistently from year to year from 0.3 per cent in 1989 to 2.9 per cent in 1995 (Table 5.2). Resistance to erythromycin increased from 3.3 per cent to 10.9 per cent over the same period (Table 5.2).

Multi-resistance strains are a problem. Of 1,751 penicillin-resistant isolates tested in the ARU between 1993 and 1995, 36 per cent were cross-resistant to erythromycin (another first line drug), and many were also resistant to other agents (Table 5.3), including tetracycline and/or chloramphenicol. The fact that penicillin-resistant pneumococci are more often resistant to other drugs than are penicillin susceptible strains has been noted by others both in the UK and elsewhere.

5.3 Other UK prevalence data

In addition to national surveillance, local UK prevalence rates for penicillin resistance in pneumococci have also been investigated (Table 5.3). These studies have mostly entailed analysis of susceptibility data for all pneumococci isolated in a particular hospital. Such studies, in different geographical locations over extended time periods, have consistently shown an increasing prevalence of penicillin resistance (Table 5.4). In 1995, the prevalence rates at one London hospital was 12 per cent, which is considerably higher than the national average. This highlights regional variation as an important component of the epidemiological picture.

5.4 Resistance in other countries

Although prevalence rates for resistance to penicillin and resistance to erythromycin are increasing in the UK, they are currently lower than in many other parts of the world (Table 5.5). However, the lower UK rates should not give rise to complacency; resistance rates comparable to those seen currently in the UK were noted in France

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[Continued

between 1984 and 1987, but thereafter increased dramatically to 20 per cent by 1992. Such swift increases often indicate clonal spread of resistant strains and this is dramatically illustrated by events in Iceland from 1989 onwards. Until that year rates of resistance were ≤ 1 per cent, subsequently they rose steadily to reach 20-25 per cent by 1993. This increase apparently reflected strains imported from Spain by returning holiday-makers and the dissemination of these organisms in child-care facilities (Soares *et al. Journal of Infectious Diseases* 168: 158-63).

5.5 The prospects for new antibiotics

Several new antimicrobials with activity against pneumococci are under development and evaluation. These include the new quinolones spar-floxacin, levofloxacin, trovofloxacin and grepafloxacin; the streptogramin quinupristin/dalfopristin (Synercid[®]); two novel ketolides, and the trimethoprim-sulfamethoxazole. Most of these agents will be appropriate for use in RTI or bacteraemia and only trovofloxacin seems likely to be suitable for use in CNS infections—where pneumococcal resistance presents the greatest clinical challenge. Vaccines offer an alternative and promising approach. However the difficulty is to devise a preparation protective against all of the 70 different pneumococcal serotypes. Vaccines presently give cover against 23 serogroups/types while those under development target 5, 7 or 9 of the most prevalent types and one must fear that their use will provide an ecological niche for presently-rarer types to fill and exploit.

TABLE 5.1

Prevalence of antibiotic resistance in pneumococci investigated in two PHLS surveys in 1990 and 1995

Antibiotic	Prevalence (per cent) of resistance	
	1990	1995
Penicillin	1.5	3.9
Erythromycin	2.8	8.6
Tetracycline	5.0	5.1
Vancomycin	0	0
Rifampicin	0	0

Source: Johnson *et al.*, 1996. *British Medical Journal* 312: 1454-56.

TABLE 5.2

Prevalence of resistance in pneumococci from blood and CSF in England and Wales, 1989-1995

Antibiotic	Prevalence (per cent) of resistance						
	1898	1990	1991	1992	1993	1994	1995
Penicillin	0.3	0.5	0.7	1.9	1.7	2.5	2.9
Erythromycin	3.3	5.1	6.4	8.6	10.8	11.2	10.9

Source: Aszkenasy *et al* 1995 *CDR Review* 5: R45-50.

Anon. 1995 *CDR* 5: 187-8.

TABLE 5.3

Resistance to other antibiotics among penicillin-resistant pneumococci¹ tested in the PHLS Antibiotic Reference Unit between 1993 and 1995

Resistance pattern	Per cent resistant
Pen/Ery	8.7
Pen/Tet	8.2
Pen/Ery/Tet	10.9
Pen/Ery/Chl	0.8
Pen/Tet/Chl	11.3
Pen/Ery/Tet/Chl	16.6

¹ Penicillin-resistant isolates accounted for 43.9 per cent of all pneumococci received by ARU in this period.

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TABLE 5.4

Prevalence of resistance to penicillin in hospitals in different regions of the UK at different times

Region	Year	Resistant Per cent
Belfast	1988	0.8
Belfast	1990	1.0
Belfast	1993	0.9
Belfast	1994	3.1
Belfast	1995	10.6
Birmingham	1989-90	0.8
Birmingham	1990-91	1.2
Birmingham	1991-92	2.9
Birmingham	1992-93	1.5
Birmingham	1993-94	8.0
London	1992-93	2.0
London	1994-95	12.0
Liverpool	1987-88	1.4
Liverpool	1988-89	2.5
Liverpool	1995	7.5

TABLE 5.5

Rates of resistance to penicillin among pneumococci from several European countries

Country	Year(s)	Resistance Per cent
Italy	1993	0.8
Belgium	1983-88	1.5
Finland	1988-90	1.9
Germany	1979-80	6.8
Iceland	1991	9.6
Romania	1991	25.0
Poland	1975	26.7
Spain	1989	44.3
Hungary	1988-89	57.8

6. RESISTANCE IN GRAM-NEGATIVE RODS

6.1 Introduction

Rates of resistance vary widely among these species: *Escherichia coli* is the commonest Gram-negative rod from clinical specimens and is amongst the least resistant; *Enterobacter* spp., *Klebsiella* spp., *Pseudomonas aeruginosa* and *Acinetobacter* spp., important hospital opportunists show greater inherent or acquired resistance. Rates of resistance also vary within species, being greatest where antibiotic usage is highest. This is illustrated in Table 6.1, comparing *P. aeruginosa* isolates from out-patients, general in-patients, and those in ICUs. Isolates from the ICU patients were more often resistant than those from other groups.

Many resistances in Gram-negative rods are plasmid-mediated and transferable allowing dissemination among species. This is true of most resistance to penicillins, trimethoprim, tetracycline, chloramphenicol and aminoglycosides. Cephalosporin resistance, too, is increasingly plasmidic. In other cases, resistance mostly arises by chromosomal mutation: examples include resistance to quinolones (e.g., ciprofloxacin), to cephalosporins in *Enterobacter* and *Citrobacter* spp. and to carbapenems in *P. aeruginosa*. Mutations cannot, like plasmids, spread directly, but mutational resistance is a concern because it can be selected during therapy in the individual patient, causing clinical failure. This risk is as high as 15-20 per cent during cephalosporin treatment of *Enterobacter* bacteraemia or pneumonia or imipenem treatment of pseudomonal disease. Gratuitous exposure may also select resistance: *Enterobacter* bacteraemias (presumably originating from the patients' own gut flora) were three-fold more likely to be cephalosporin-resistant if the patient had recently received a cephalosporin. Mutations can also affect plasmid-borne genes: the major example concerns extended-spectrum β -lactamases. Plasmid-mediated

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“TEM” and “SHV” β -lactamases have long been the major sources of resistance to penicillins in Gram-negative bacteria. During the 1970s and 80s, major effort was put into developing cephalosporins stable to these enzymes; but their subsequent use has selected mutant TEM and SHV enzymes with cephalosporin-hydrolysing activity. These are increasingly frequent.

Individual resistances are reviewed below but, increasingly, the problem is of multi-resistance: isolates resistant to one antimicrobial are more likely to be resistant also to others. This is illustrated in Table 6.2, showing that *Klebsiellae* with extended spectrum β -lactamases were more often cross-resistant to quinolones and aminoglycosides than those without these enzymes.

6.2 The UK situation

Rates of resistance to commonly-used antimicrobials are summarised in Table 6.3. These data are for isolates from blood and CSF specimens in England and Wales between 1989 and 1994 as reported to CDSC. Except for ampicillin and trimethoprim, most of the agents listed retained good activity against the major species. Retention of good activity by gentamicin, an agent available since 1963, is especially striking.

Detailed examinations, however, reveals more disturbing features:

- (i) In several species there is a statistical trend towards increasing resistance, especially to cephalosporins and trimethoprim;
- (ii) looking back 15-20 years, ceftazidime and ciprofloxacin were active against >99 per cent of *E. coli*, *Klebsiella* and *Enterobacter* isolates, not the 90-95 per cent seen now; and
- (iii) the favourable overall picture does not help those units where (multi)-resistant organisms are frequent—as in many ICU's (a.v. Table 6.1). In the worst case, some *Acinetobacter* isolates from UK patients are resistant to all antibiotics.

6.3 UK situation compared to that overseas

The rates of resistance in the UK are low by international standards. Rates are even lower in the Scandinavian countries and the Netherlands, similar to the UK in Germany, Austria and Switzerland but higher in Southern Europe, much of Asia and the Americas. The highest rates are often in the more-prosperous developing countries, e.g., in SE Asia, Turkey and Argentina. Rates of resistance amongst Gram-negative rods in the USA are summarised in Table 6.4, for comparison to Table 6.3 showing UK rates. The low rates of gentamicin resistance in the UK have been remarked already and are two-to-three-fold below those for US isolates in the same period. At a further extreme it is common to see 20-40 per cent resistance to gentamicin amongst Gram-negative rods isolated from patients in tertiary hospitals in Southern Europe, Japan and the Americas.

The rates of resistance to ciprofloxacin and ceftazidime among the UK isolates (Table 6.3) mostly also compare favourably to those in the US (Table 6.4), which, themselves, are lower than in countries where antimicrobial use is essentially unrestricted. A 1992 survey found 70 per cent of the *Enterobacter* isolates from Athens hospitals resistant to ceftazidime, and up to 60 per cent of *E. coli* are resistant to ciprofloxacin in India. Greece has long had a notorious reputation for antibiotic resistance; in the case of ciprofloxacin in India, multiple “pirated” brands are available over-the-counter, some of low potency and all (owing to cost) prone to be under-dosed.

Higher overseas rates of resistance should concern us: first because they show what can happen when antibiotic use is uncontrolled and, secondly, because patients infected abroad are returned or referred to the UK. I (DML) am aware of importations of unusual cephalosporin-resistant *Klebsiellae* from India to Leeds and to Birmingham and of multi-resistant *Acinetobacter* from Crete to York and Spain to Burnley. The import and spread of multi-resistant pneumococci from Spain to Iceland is outlined elsewhere in this document.

6.4 Combating resistance in Gram-negative bacteria

So far new antibiotics have “kept ahead” of resistance in Gram-negative bacteria. As resistance spread to penicillins and trimethoprim, cephalosporins were developed; as resistance to cephalosporins developed, emphasis switched to carbapenems and quinolones. Now however, there is no new anti-Gram-negative class in advanced development. This is disturbing because ciprofloxacin resistance, though infrequent in the UK (Table 3), is widely scattered and carbapenem resistance is beginning to emerge in *Acinetobacter* spp. worldwide. Vaccines are not an answer to nosocomial Gram-negative rods because of the diversity of species involved, some of them components of the healthy gut flora, and because of the difficulty of deciding whom to vaccinate. In the absence of new therapies, the best hopes of containing the problems of resistance in Gram-negative bacteria must lie in minimising the spread of resistance and the incidence of cross-infection by resistant bacteria. These aspects are covered below and the comments relate widely, not just to Gram-negative bacteria.

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6.5 Antibiotic usage

In the absence or paucity of new antibiotics our best answer lies in careful use of those we do have. Critical measures include:

- (i) minimising total antibiotic use;
- (ii) avoiding antibiotics that are prone to select mutational resistance in particular pathogens;
- (iii) design of antibiotic policies such that the first-line agent does not select resistance to the reserve agent; and
- (iv) prevention of cross-infection. Major educational efforts are needed to stress these subjects to prescribers.

Those countries with conservative antibiotic usage—Scandinavia, Holland and the UK—have the lowest rates of resistance, whereas those where use is heavy and unrestricted have greater problems. We should be guided by these empirical observations, not by unproven propositions on antibiotic rotation or combination. The proponents of antibiotic rotation argue that cycling a hospital's antibiotic policy every few months should prevent the accumulation of resistance to one antimicrobial but ignore:

- (i) the increasing role of multi-resistance;
- (ii) the fact that single plasmids can determine resistances to many agents, any one of which will conserve the whole plasmid; and
- (iii) that antibiotic choice is often dictated by existing resistance. Proof of the efficacy of rotation is lacking and streptomycin resistance remains common (20 per cent of UK *E.coli*) despite 30 years of virtual disuse. Combination therapy can often be justified as achieving synergy but, except with tuberculosis, its effectiveness in preventing resistance is doubtful.

6.6 Surveillance of resistance

In the present situation, where the emergence of resistance is out-pacing that of new antimicrobials, close monitoring of the situation is desirable. To address this situation the PHLS represented by ARU and CDSC has a joint initiative with the British Society for Antimicrobial Chemotherapy (BSAC) aiming to establish a surveillance network based around improved susceptibility testing and data analysis. Specific objectives are to:

- (i) Identify changing trends in the incidence of resistance and to provide early warning of the emergence and spread of new types of resistance.
- (ii) Detect reduced susceptibility, which is often an early indicator of developing resistance, but which is prone to be missed in present reporting systems.
- (iii) To allow recognition of hospital-to-hospital or regional differences in resistance and, if possible, to relate these to drug usage patterns.
- (iv) To permit clear insight into where new (and, generally, expensive) antibiotics do, or do not, merit use owing to prevalent resistance to older agents.

TABLE 6.1

Resistance (per cent) in UK isolates of P. aeruginosa, by patient type

	ICU patients (n=134)	Isolates from General in-patients (n=1,042)	Out-patients (797)
Gentamicin	² 18.6	11.3	10.8
Amikacin	¹ 15.6	9.5	10.2
Ciprofloxacin	² 15.6	8.4	6.6
Ceftazidime	² 20.1	11.0	² 6.0
Carbenicillin	² 21.6	12.7	² 8.5
Azlocillin	² 24.6	13.1	² 5.5
Imipenem	9.7	1.9	2.1
Meropenem	6.7	0.8	0.6

Note: Significance of any difference from general in-patient group ¹p<0.05; ²p<0.01.

Source: Survey of Chen *et al.*, 1995. *Journal of Antimicrobial Chemotherapy*. 35, 521-34.

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TABLE 6.2
Multi-resistance amongst *Klebsiella* spp. in a European survey

	Gentamicin 1mg/L	Per cent also resistant to: Amikacin 4mg/L	Ciprofloxacin 1mg/L
Cephalosporin-resistant ESBL-positive (n=220)	74	52	33
Cephalosporin-susceptible ESBL-negative (n=675)	5.8	1.1	2.5

Source: survey of Livermore & Yuan 1996, *Journal of Antimicrobial Chemotherapy*, 38, 409-24.
Isolates were from ICUs at 35 hospitals, with no more than 46 isolates from any one hospital.

TABLE 6.3
Resistance of Gram-negative rods from blood and CSF, England and Wales 1989-94

Resistance	1989	1990	1991	1992	1993	1994
<i>E. coli</i>						
Gentamicin	1.5	1.7	1.7	1.6	1.5	1.6
Ampicillin	54.7	54.8	54.3	52.9	54.2	55.3
Cefuroxime	7.2	6.3	6.8	6.1	8.6	7.1
Ceftazidime	1.2	1.0	0.9	1.3	1.3	1.2
Ciprofloxacin	0.5	0.8	0.7	0.9	1.2	1.7
<i>Klebsiella</i> spp						
Gentamicin	4.1	2.7	2.5	3.0	3.3	3.7
Cefuroxime	12.1	11.9	12.8	11.3	12.9	13.5
Ceftazidime	2.7	4.2	3.6	5.2	4.4	5.7 ¹
Ciprofloxacin	2.9	3.8	4.4	4.8	5.9	6.5 ¹
Trimethoprim	21.0	23.9	21.4	22.2	29.0	27.1 ¹
<i>Enterobacter</i> spp						
Gentamicin	3.0	2.6	2.4	2.7	3.5	3.5
Cefuroxime	36.8	46.3	43.3	43.2	45.8	49.2
Ceftazidime	19.2	21.6	21.8	23.2	24.8	26.5
Ciprofloxacin	1.9	2.2	4.1	4.7	4.9	7.1
Trimethoprim	18.3	19.1	20.0	23.6	25.0	21.8
<i>Pseudomonas aeruginosa</i>						
Gentamicin	8.1	7.3	7.3	5.4	5.0	6.1
Azlocillin	8.2	5.2	8.6	5.2	9.4	5.9
Ceftazidime	5.0	4.7	4.9	3.7	6.7	5.3
Ciprofloxacin	4.7	6.5	6.8	6.7	8.6	7.3

¹ Significant at $p < 0.05$. From Speller *et al* 1997, *Clinical Microbiology & Infections*, 3 (suppl 2) 179.

TABLE 6.4
Resistance of Gram-negative rods, USA 1989-94

	1989	1990	1991	1992	1993	1994
<i>E. coli</i>						
Gentamicin	2.3	2.9	3.8	3.2	3.4	3.5
Ampicillin	27.6	30.6	32.3	33.1	36.4	38.4
Ceftazidime	1.3	0.9	1.6	1.5	1.3	1.6
Ciprofloxacin	0.3	0.2	0.2	0.6	1.1	1.4
<i>Klebsiella</i> spp						
Gentamicin	5.6	7.7	12.1	8.1	12.4	13.0
Ceftazidime	12.1	11.9	12.8	11.3	12.9	13.5
Ciprofloxacin	1.0	2.3	8.4	6.6	8.6	6.4

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	Per cent resistance					
	1989	1990	1991	1992	1993	1994
<i>Enterobacter spp</i>						
Gentamicin	7.1	9.4	9.4	7.2	6.2	6.0
Ceftazidime	34.8	38.7	37.5	38.8	36.4	35.8
Ciprofloxacin	2.8	2.1	3.1	3.8	4.5	4.4
<i>Pseudomonas aeruginosa</i>						
Gentamicin	14.6	13.5	16.4	13.0	9.5	9.7
Ceftazidime	11.4	9.8	8.7	7.9	8.7	7.8
Ciprofloxacin	4.4	3.6	4.8	6.2	7.6	10.0

Data are taken from: Wiedmann & Grimm 1996. Chapter 19 in Lorian, Antibiotics in Laboratory Medicine. p. 900-1168. Williams & Wilkins, Baltimore.

7. ANTIBIOTIC RESISTANCE IN BACTERIAL ENTERIC PATHOGENS IN ENGLAND AND WALES

This submission contains some unpublished material. The data, now published elsewhere, should not be quoted in other publications without permission from the Public Health Laboratory Service.

Glossary

Abbreviations for resistance to antimicrobial drugs

A	ampicillin
C	chloramphenicol
Co	colomycin
Cp	ciprofloxacin
E	erythromycin
Fu	furazolidone
G	gentamicin
K	kanamycin
Mz	metronidazole
Nx	nalidixic acid
S	streptomycin
Su	sulphonamides
T	tetracyclines
Tm	trimethoprim
DR	drug-resistant (=resistance to one or more antimicrobial drug)
MR	multiresistant (=resistance to four or more drugs)
R-type	resistance type
PT	phage type
DT	definitive phage type
VTEC	Vero cytotoxin-producing <i>Escherichia coli</i>
VPC	Veterinary Products Committee

7.1 Overview

At present multiple drug resistance is not a significant problem in *Campylobacter*, *Yersinia*, *Listeria* and Vero cytotoxin-producing *Escherichia coli* O157. However it is a major problem in *Salmonella*, particularly *S. typhimurium*. Resistance to the fluoroquinolones is an emerging problem in some salmonella serotypes, particularly *S. typhimurium*, *S. virchow* and *S. hadar*, and in *Campylobacter* spp.

The overuse of antimicrobial drugs in animal husbandry is a key factor in the emergence and persistence of drug resistant foodborne bacterial enteric pathogens. Legislation following the Swann Report resulted in the banning of the use of human therapeutic antibiotics as growth promoters in animal husbandry. In 1992 the Lamming Committee recommended that the prophylactic use of antibiotics giving cross-resistance to those used

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in human medicine should be reconsidered. The Veterinary Products Committee (VPC) recommended that the prophylactic use of "new" antibiotics should be discouraged but that they would consider each case on its merits. At the end of 1993 the VPC approved the use of enrofloxacin in animals in the UK, despite information from the Netherlands that its use in poultry had contributed to the emergence of ciproflaxacin-resistant campylobacters in that country.

In 1994 the WHO Scientific Working Group on the Monitoring and Management of Bacterial Resistance to Antimicrobial Agents commented that "the increase in the number of drug-resistant bacteria has not been matched by a parallel increase in the arsenal of antimicrobial agents used to treat infections" (WHO, 1995). They stated that "new" antimicrobial agents are unlikely to be developed for several years and that "the use of antimicrobial agents in animal husbandry, particularly for growth promotion and prophylaxis of infection, provides an additional selective pressure which encouraged the emergence of drug-resistant organisms". In particular, in the development of strategies to decrease the emergence and dissemination of resistant organisms in veterinary medicine and the environment, they recommended that the unnecessary use of therapeutic antimicrobials for prophylaxis in food animals should be discouraged, and that antimicrobial agents should not be used as a substitute for adequate hygiene in animal husbandry.

7.2 Introduction

This memorandum discusses resistance to antimicrobial drugs in the following bacteria: *Salmonella* spp; *Campylobacter* spp; *Yersinia* spp; *Listeria* spp; Vero cytotoxin-producing *Escherichia coli* 0157.

Drug resistance in bacterial enteric pathogens is either constitutive (e.g. resistance to malidixic acid in *Listeria* spp) or induced as a result of exposure to antibiotics when used in human medicine, veterinary medicine or agriculture.

Plasmids coding for drug resistance can be acquired *in vivo* during the course of an infection in humans during antibiotic therapy and although this can be important for the individual patient, the epidemiological consequences are minimal in developed countries.¹ However, in developing countries the overuse of antibiotics in human medicine has been important in the emergence and spread of multiresistant strains of *Salmonella*. Examples are *S. wien* and *S. typhimurium*, which have caused numerous outbreaks of serious disease both in hospitals and the community over wide geographical areas (for review, see Rowe and Threlfall).²

In the UK the majority of pathogenic enterobacteria of epidemiological importance are zoonotic in origin and drug resistance is acquired *in vivo* in the food animal before transmission of the organism to humans via the food chain. For example, the high incidence of resistance in isolates of the epidemiologically-important *S. typhimurium* phage types DTs 204c and 104 from food animals has recently been highlighted by Wray and Davies.³

Whether drug resistance in bacterial enteric pathogens which are transmitted to humans through the food chain is a public health problem has been a contentious issue since the late 1960s. In 1969 the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (the Swann Committee) concluded that "it is clear that there has been a dramatic increase over the years in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics. Further, these resistant strains are able to transmit their resistance to other bacteria. This resistance has resulted from the use of antibiotics for growth promotion and other purposes in farm livestock".⁴ As a result of this report legislation was enacted which banned the use of antibiotics used in human medicine as growth promoters in food animals. However, no restrictions were made on the use of such antibiotics for prophylaxis or therapy in animal husbandry or veterinary medicine.

In 1992 the Expert Group on Animal Feedingstuffs (the Lamming Committee) recommended that "not only should antibiotics giving cross resistance to those used in human medicine not be used as growth promoters but that their prophylactic use in animals be reconsidered".⁵ The Government response recommended that the advice of the VPC and the Committee on the Safety of Medicines be sought, and in 1992 the VPC recommended that new antibiotics should not necessarily be precluded from therapeutic use in animals but that their prophylactic use should be discouraged. The VPC also stated that it would consider each case on its merits and seek appropriate advice.⁶ At the end of 1993 the VPC approved the use of enrofloxacin in animals in the UK despite the evidence which was already available from the Netherlands demonstrating that the use of this antibiotic in poultry resulted in an upsurge in the incidence of ciproflaxacin-resistant campylobacters in poultry and humans (see below).

In this memorandum we present evidence which demonstrates that the emergence and spread of drug-resistant enterobacterial pathogens is an unwelcome but inevitable consequence of the overuse of antibiotics. For the zoonotic bacterial pathogens this overuse occurs in food-producing animals, and in the UK this is the all important factor.

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7.3 *Salmonella*

7.3.1 Background

Since 1990 approximately 30,000 isolates per annum of salmonella from humans in England and Wales have been referred to the LEP (Figure 7.2). Salmonellosis is caused by more than 2,200 different salmonella serotypes, which can be classified according to their adaptation to human and animal hosts:

- Group 1 causes enteric fever in human and higher primates, e.g. *S. typhi*, *S. paratyphi*. As organisms causing enteric fever are not zoonotic in origin, drug resistance in isolates of *S. typhi*, *S. paratyphi* A and *S. paratyphi* B has not been included in the following analyses.
- Group 2 causes disease in specified animals, e.g. *S. dublin*—cattle, *S. cholerae-suis* pigs, but only infrequently in humans. However, when these serotypes cause disease in humans, it is frequently invasive and can be life-threatening.
- Group 3 includes the remaining 2,000+ serotypes. Typically, such serotypes cause enteritis which is often mild and self-limiting but can be severe in the young, the elderly and patients with other complications. The group includes *S. enteritidis*, *S. typhimurium*, *S. virchow* and *S. hadar*, the four most important zoonotic serotypes in human salmonellosis in England and Wales (Table 7.1).

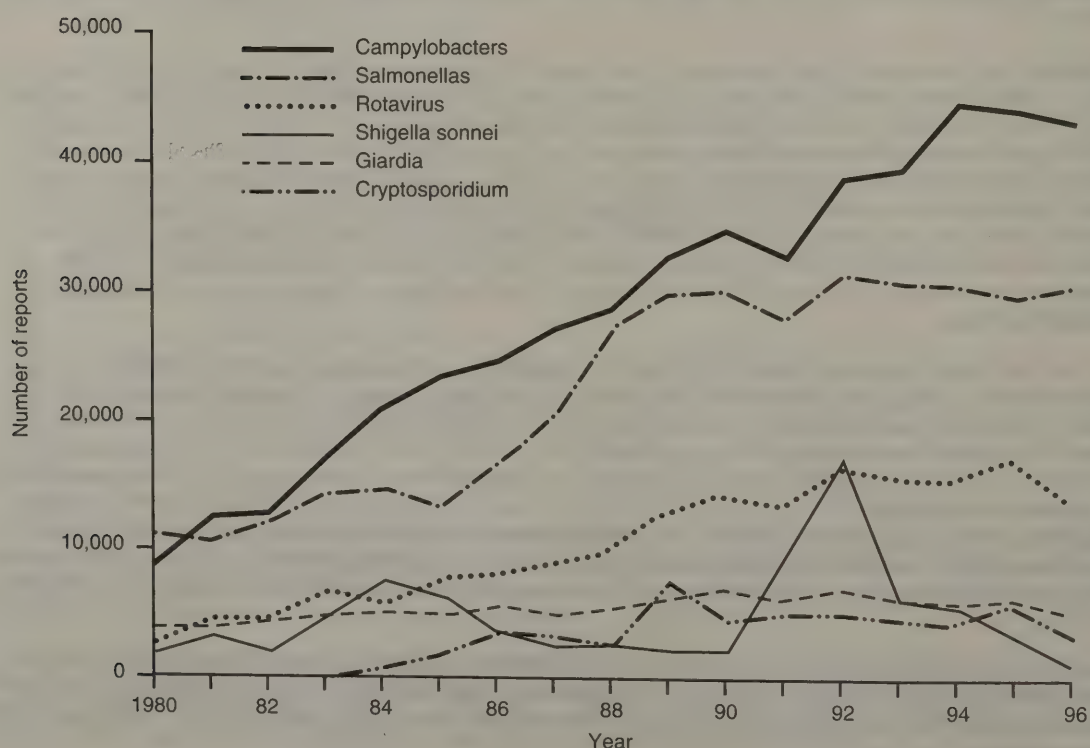
7.3.2 LEP Studies—Humans and food animals

1965–74

From 1964–68 there was an extensive epidemic of multiresistant *S. typhimurium* DT 29 in bovine animals and humans in the UK.⁷ As a result of this epidemic and following widespread concern about the use of antimicrobials for growth promotion in food animals in 1969 the Swann Committee recommended that certain antibiotics, at that time widely used in food animals without prescription as “feed” antibiotics, should be available only on the same terms as a scheduled antibiotic, i.e., only on prescription, and should not be used for growth promotion.⁴ A further recommendation of the Swann Committee was that certain antibiotics used in human medicine (e.g. chloramphenicol) should be reserved for use in veterinary medicine specifically for special situations. Appropriate legislation followed and by 1970 DT 29 was uncommon in bovine animals in Britain. For the next six years only about 8 per cent of all salmonella strains from cattle and 3 per cent of strains from humans were multiresistant.²

Figure 7.2

Laboratory Reports of Selected Gastrointestinal Infections England and Wales 1980 - 1996



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[Continued

Multiple drug resistance in salmonellas from humans

Figure 7.3



TABLE 7.1

Salmonella serotypes—human—England and Wales 1996

Rank	Serotype	No.	Per cent DR	Per cent MR
1.	<i>S. enteritidis</i>	18,968	9	0.5
2.	<i>S. typhimurium</i>	5,849	90	81
3.	<i>S. virchow</i>	1,260	76	19
4.	<i>S. hadar</i>	633	94	54
5.	<i>S. newport</i>	223	47	15
6.	<i>S. heidelberg</i>	219	38	18
7.	<i>S. infantis</i>	201	47	8
8.	<i>S. indiana</i>	170	21	5
9.	<i>S. agona</i>	136	21	10
10.	<i>S. braenderup</i>	133	5	1
Total 10 serotypes		27,792	32	20
Total remaining serotypes		2,283	22	7
Total all serotypes		30,075	31	19

1975–90

From 1975 to the mid 1980s there was again a substantial upsurge in the incidence of multiresistant *S. typhimurium* from food animals, particularly bovines and a concurrent increase in multiresistant isolates from humans. The phage types involved were different from those observed in the 1960s, with the related phage types DTs 204, 193 and 204c predominating.⁸⁻¹¹ A feature of this outbreak was the sequential acquisition of plasmids and transposons coding for resistance to a wide range of antimicrobials (ACGKSSuTTm). The acquisition of drug resistance by strains of these phage types followed the introduction and use, in calf husbandry, of at least some of the antimicrobials, in attempts to combat infections with *S. typhimurium* resistant to an increasing range of antibiotics.² In particular, this epidemic provided the first conclusive evidence of the introduction and use, in calf husbandry, of a veterinary antibiotic (apramycin) giving rise to resistance to the closely-related antibiotic gentamicin, which is used for treating severe systemic infections in humans.¹¹⁻¹³ By the end of 1990 60 per cent of isolates from cattle were multiresistant.¹⁴⁻¹⁵

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1991-94

From 1991-94 there was a further substantial increase in the incidence of drug resistance in *S. typhimurium* and by 1994 62 per cent of isolates were multiresistant (Figure 7.3).¹⁶ An important factor in this increase was the epidemic spread since 1990 of multiresistant *S. typhimurium* DT 104 (= DT 104) with chromosomally-encoded drug resistance (R-type ACSSuT) in bovines in Britain.¹⁷⁻²⁰ Also of note in 1994 was a significant increase in both drug resistance and multiple drug resistance in the poultry-associated serotypes *S. virchow* and *S. hadar*, with a substantial proportion of isolates resistant to ciprofloxacin (MIC: >0.125 mg/L).¹⁶

TABLE 7.2

Incidence of drug resistance in non-typhoidal salmonellas isolated from humans in England and Wales in 1994 and 1996

Serotype	Total	1994		Total	1996	
		Per cent DR	Per cent MR		Per cent DR	Per cent MR
<i>S. enteritidis</i>	17,701	9	0.4	18,968	8	0.5
<i>S. typhimurium</i>	5,603	78	62	5,849	90	81
<i>S. virchow</i>	2,797	71	9	1,260	76	19
<i>S. hadar</i>	753	90	13	633	94	56
Others	4,293	28	10	3,365	25	9
(219 serotypes)				(250 serotypes)		

Figures for 1996 are provisional.

TABLE 7.3

Resistance to individual antimicrobials (per cent)

Antimicrobial	<i>S. enteritidis</i>		<i>S. typhimurium</i>		<i>S. virchow</i>		<i>S. hadar</i>	
	1994 (n=17701)	1996 (n=18968)	1994 (n=5603)	1996 (n=5849)	1994 (n=2797)	1996 (n=1260)	1994 (n=753)	1996 (n=633)
Ampicillin	5	5	59	80	11	26	31	59
Chloramphenicol	<1	<1	54	75	4	7	0	<1
Gentamicin	<1	<1	1	1	1	<1	<1	<1
Kanamycin	<1	<1	2	3	2	16	7	4
Streptomycin	1	1	62	81	7	7	85	84
Sulphonamides	2	1	71	86	27	25	12	10
Tetracyclines	2	2	72	86	9	16	81	83
Trimethoprim	<1	<1	18	32	27	26	7	8
Furazolidone	1	<1	3	2	52	48	<1	<1
Ciprofloxacin	0.4	0.8	1	12	5	10	40	60

1995-1996

From 1993 isolates of *S. typhimurium* from food animals have been phage typed at the Central Veterinary Laboratory and detailed results are not published. In 1996 the four major serotypes from human cases of salmonellosis were *S. enteritidis*, *S. typhimurium*, *S. virchow* and *S. hadar*, comprising 89 per cent of non-typhoidal salmonellas referred to LEP (Table 7.1). For *S. enteritidis* there has been little change in the overall low incidence of drug resistance. The *S. enteritidis* phage type in which resistance was most common was PT 6A and a high proportion of drug-resistant strains of this phage type were from cases with a history of recent foreign travel, notably to Greece, the Greek islands, Spain and Turkey.²¹ For *S. typhimurium* 80 per cent of isolates received in 1996 were multiresistant (Table 7.2). Isolates of multiresistant DT 104 have continued to increase (Figure 7.4). The organism is now established in other food animals including poultry, sheep and pigs,^{3, 22} and has been isolated from a wide range of human foods.^{18, 23} Since 1994 strains of DT 104 with additional plasmid-encoded resistance to sulphonamides and trimethoprim (SuTm) have become common, and multiresistant strains with additional chromosomally-encoded resistance to ciprofloxacin have also increased in incidence (Figure 7.5).²⁴ For *S. virchow* multiple resistance is concentrated in two phage types, PTs 47 and 31. Within these phage types, a high proportion of multiresistant isolates were from patients with a history of recent foreign travel. Because of the invasive potential of *S. virchow* in humans,²⁵ drug resistance is of therapeutic importance. In 1996 11 per cent of isolates of *S. virchow* were ciprofloxacin-resistant and resistance to this antimicrobial is now common in phage types 8 and 26 which are endemic in England and Wales. For *S. hadar*, 56 per cent of isolates received in 1996 were multiresistant, with the majority of multiresistant isolates also

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resistant to ciprofloxacin (Table 7.3). Most patients with multiresistant isolates did not provide a history of recent foreign travel.

The fluoroquinolone antibiotic enrofloxacin was licensed for veterinary use in the UK in November 1993 and is now extensively used in food animals, particularly poultry. Danofloxacin, another fluoroquinolone antibiotic, was introduced into veterinary practice in 1996 specifically for the treatment of respiratory and enteric disease in food animals. Since the licensing of enrofloxacin for veterinary use, there has been a substantial increase in resistance to ciprofloxacin in the poultry-related serotypes *S. hadar* and *S. virchow* and also in multiresistant *S. typhimurium* DT 104.

7.3.3 LEP studies—isolates from food

Between 1991 and 1996 LEP examined 7,952 salmonellas from food of which the majority [5975, 75.1 per cent] were in the five major food categories detailed below. These included isolates from a number of PHLS surveys as well as foods associated with outbreaks or sampled during routine surveillance. Within these five categories *S. typhimurium* and *S. enteritidis* accounted for 35 per cent and 28 per cent of isolates respectively. The distribution of resistance is summarised in Table 7.4.

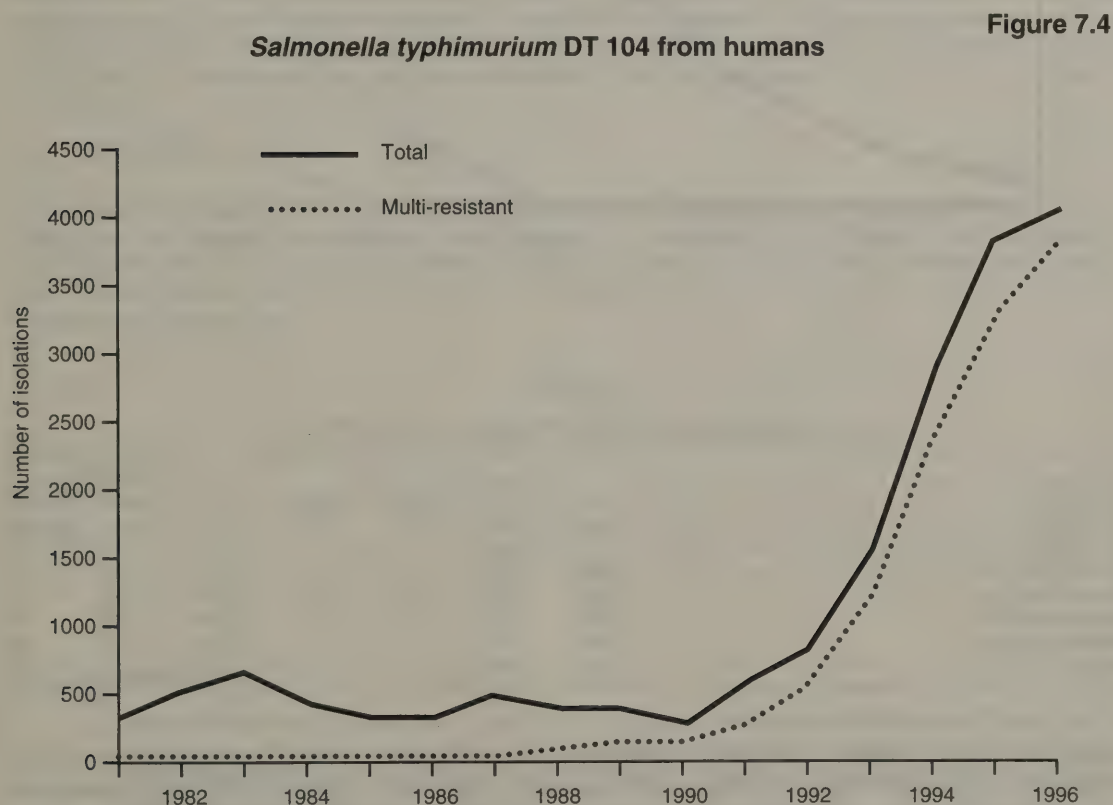


Figure 7.5

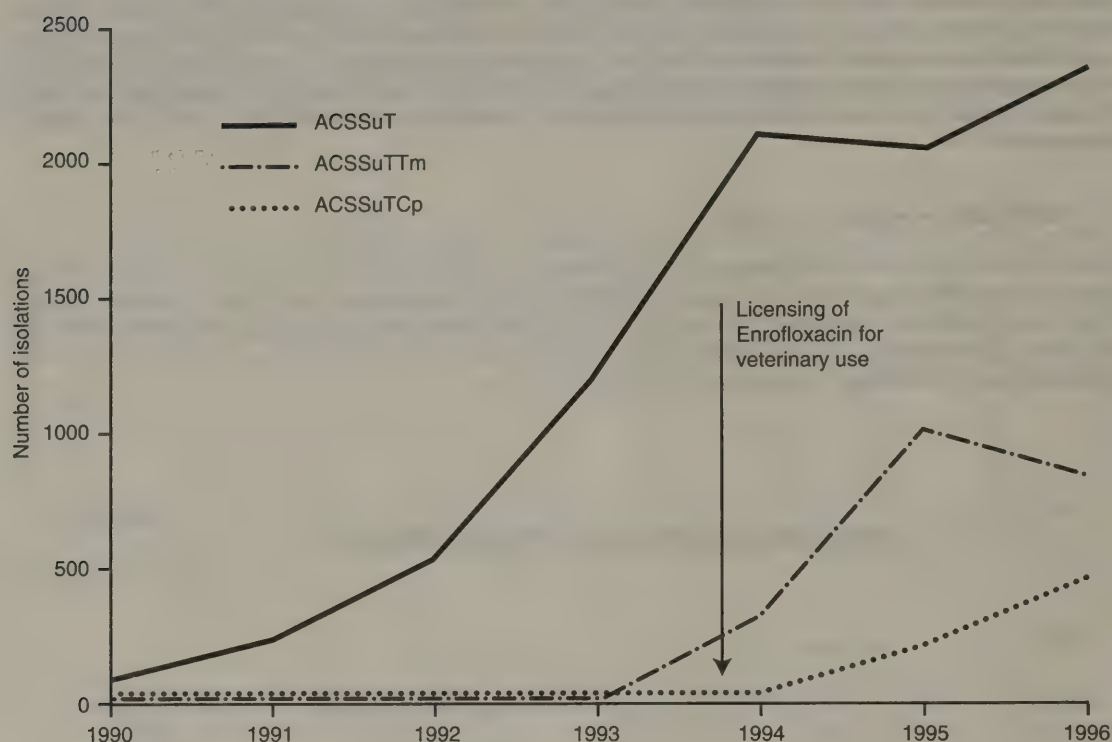
R-types in *Salmonella typhimurium* DT 104 from humans

TABLE 7.4

S. enteritidis and *S. typhimurium* from food; 1991–96

Food category	Total	Total	<i>S. enteritidis</i>		Total	<i>S. typhimurium</i>	
			Per cent	Per cent		Per cent	Per cent
			DR	MR		DR	MR
Eggs and egg products	1,144	735	7	0	187	27	4
Chicken meat	2,479	624	13	0.6	249	65	49
Carcass meat/offal	549	65	5	2	484	92	71
Mince/burgers/pie	285	99	12	0	94	84	60
Sausages	1,300	68	6	0	960	92	48

Resistance was rare among salmonellas from eggs and egg products reflecting the predominance of *S. enteritidis* PT 4. There was a higher incidence of resistance in chicken meat, where a wider range of serotypes was encountered, including multiresistant *S. typhimurium* DT104. Salmonellas from carcass meat and meat products were predominantly *S. typhimurium* and a majority of isolates were multiresistant. The lower incidence of multiresistance in isolates from sausages could be explained by the inclusion of other meat, e.g., pork meat, in which *S. typhimurium* DT 208, which is resistant to only three drugs [Su, T and Tm], was common.

7.3.4 Conclusions

- Multiple drug resistance is now prevalent in the epidemiologically-important zoonotic serotypes *S. typhimurium*, *S. hadar* and *S. virchow*.
- Since 1990 there has been an epidemic of multiresistant *S. typhimurium* DT 104 in bovine animals and the organism is now established in other food animals including poultry. Multiresistant *S. typhimurium* DT 104 has been transmitted through the food chain to humans.
- The use of fluoroquinolones and trimethoprim in food animals has contributed to the development of resistance to these antibiotics in zoonotic salmonellas.

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7.4 *Campylobacter*

7.4.1 Background

Of 2,209 campylobacters isolated from humans in the Plymouth area in 1991 4 per cent were ciprofloxacin-resistant and 33 per cent of patients with ciprofloxacin-resistant isolates had recently travelled abroad.²⁶ A similar study conducted in Hampshire in 1995 identified an overall ciprofloxacin resistance incidence of 13 per cent. Forty-one per cent of patients with a history of recent foreign travel had ciprofloxacin-resistant campylobacters compared to only 6 per cent of patients infected in the UK.²⁷ In Oxfordshire the incidence of ciprofloxacin-resistant campylobacters increased from 3 per cent in 1991 to 7 per cent in 1995. Half of the patients have no history of recent foreign travel and since quinolones are rarely prescribed by GPs in that area, it was concluded that the increasing use of quinolone drugs in poultry was the more likely explanation for this increase.²⁸

In the UK in 1995, 3 of 123 [2 per cent] *C. jejuni* isolates from poultry were found to be resistant to enrofloxacin.²⁹ Among isolates from retail chicken carcasses only one of 37 UK-bred birds had ciprofloxacin-resistant campylobacters compared to seven of 26 imported birds.²⁶ In contrast, in another study of UK retail chickens 11 per cent of 82 campylobacter strains were found to be ciprofloxacin-resistant.²⁷

In the Netherlands between 1982 and 1989 the incidence of resistance to ciprofloxacin in *Campylobacter* spp. isolated from chickens increased from 0 per cent to 14 per cent, and was paralleled in man by an increase from 0 per cent to 11 per cent. This increase in the incidence of fluoroquinolone resistance followed the introduction and extensive use of enrofloxacin in the poultry industry in the Netherlands.³⁰ In Spain resistance rates of 18 per cent for ampicillin, 2 per cent for erythromycin, 5 per cent for kanamycin, 42 per cent for tetracyclines and 31–34 per cent for quinolones in campylobacters from humans have been reported.^{31–33}

7.4.2 LEP studies

Since April 1996 1263 isolates of campylobacter from humans in Wales have been tested for drug resistance. All isolates were constitutively resistant to trimethoprim. 89 per cent of both *C. jejuni* and *C. coli* were resistance to one or more drugs other than trimethoprim although a wide range of drug resistance patterns was identified. There were noticeable differences between the two predominant species in the incidence of resistance to colomycin and tetracyclines.

TABLE 7.5

Campylobacter spp from humans in Wales; 1996 percentage resistant to:

Species	Total	A	C	Co	E	K	T	Fu	Mz	Nx	Cp
<i>C. jejuni</i>	1,113	78	3	12	2	2	26	0.3	63	16	12
<i>C. coli</i>	150	75	2	45	10	2	15	0	51	21	19

7.4.3 Conclusion

- Human isolates of *C. jejuni* and *C. coli* are constitutively resistant to trimethoprim. The majority of isolates are also resistant to one or more additional drugs with a high proportion resistant to ciprofloxacin. Isolates from poultry also have a high incidence of ciprofloxacin resistance although information is very limited.
- Studies in the Netherlands have demonstrated an association between the use of enrofloxacin in poultry and the emergence of ciprofloxacin-resistant campylobacters in poultry and humans.

7.5 *Yersinia*

7.5.1 Background

Yersinia enterocolitica has been recovered from a wide variety of food animals and the pig is considered to be the major reservoir.³⁴ Human infection with *Y. pseudotuberculosis* is less common than infection with *Y. enterocolitica*³⁵ and during the period 1991 to 1996, LEP received 1961 isolates of *Y. enterocolitica* and five isolates of *Y. pseudotuberculosis* from cases of human infection.

There is little recent information on drug resistance in *Y. enterocolitica*. Of 150 clinical isolates from the British Isles, all were resistant to ampicillin (>32 mg/l), tetracyclines (>4 mg/l) and trimethoprim (>2 mg/l).³⁶

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The majority of *Y. enterocolitica* are intrinsically resistant to ampicillin and resistance to this drug is therefore not considered in the LEP studies. Generally, *Y. enterocolitica* isolates are reported as being susceptible *in vitro* to chloramphenicol, gentamicin, kanamycin, tetracyclines, trimethoprim-sulphamethoxazole and fluoroquinolones.^{37,38}

7.5.2 LEP Studies

Of 1,860 human isolates of *Y. enterocolitica*, only 95 (5 per cent) were found to be multiresistant (Tables 7.6, 7.7). Of 770 isolates from foods only eight (1 per cent) were multiresistant. The most common multiresistance patterns were ACSSu, ASSuTTm and ASSuTm.

TABLE 7.6
Yersinia enterocolitica 1991 to 1996

	DR per cent	MR per cent	Total
Human	90	5	1,860
Human Foods	92	1	770

TABLE 7.7
Y. enterocolitica: resistance to individual antimicrobials

	Human isolates n = 1,860 (per cent)	Food isolates n = 770 (per cent)
Ampicillin ¹	85	86
Chloramphenicol	2	2
Erythromycin	<1	2
Gentamicin	<1	0
Kanamycin	0	<1
Streptomycin	5	1
Sulphonamides	5	1
Tetracyclines	4	<1
Trimethoprim	4	<1
Furazolidone	4	7
Nalidixic acid	<1	0
Ciprofloxacin	<1	0

¹Intrinsic resistance.

7.5.3 Conclusions

Drug resistance, other than to ampicillin, is a rare phenomenon in *Y. enterocolitica* from humans or foods.

7.6 *Listeria*

7.6.1 Background

All strains of *Listeria monocytogenes* are sensitive to ampicillin.³⁹ Apart from plasmid-encoded resistance to chloramphenicol, erythromycin, streptomycin and tetracycline in a few human isolates from France and Switzerland,⁴⁰ the bacterium is sensitive to most other antibiotics but is constitutively resistant to the cephalosporins, nalidixic acid and polymyxin.⁴¹⁻⁴² A small proportion (2-5 per cent) of strains are highly resistant to tetracyclines.⁴³ In the UK the incidence of tetracycline resistance in clinical isolates of *L. monocytogenes* has remained constant over the past 30 years with between 5 per cent and 2 per cent of isolates resistant to this antibiotic.^{44,45}

7.6.2 LEP Studies

L. monocytogenes strains from 1995 and 1996 comprised 95 human and 227 food isolates. All except eight isolates showed typical resistance patterns, i.e., constitutive resistance to the cephalosporins, nalidixic acid and polymyxins. Three human isolates were either resistant to ciprofloxacin, erythromycin or tetracyclines, and five

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food isolates included two resistant to ciprofloxacin alone, two resistant to either trimethoprim or tetracyclines alone, and one isolate resistant to gentamicin, netilmicin, kanamycin, streptomycin, sulphonamides, tetracyclines and amikacin.

7.6.3 Conclusions

With the exception of constitutive resistance to the cephalosporins, nalidixic acid and polymyxins, resistance to other drugs is rare in *L. monocytogenes*. However, high level ciprofloxacin resistance has been found in the UK in a few strains from humans and from food.

7.7 Vero cytotoxin-producing *Escherichia coli* O157

7.7.1 Background

The main reservoir for VTEC of serogroup O157 (= O157 VTEC) is healthy cattle although there have been recent reports of these organisms in sheep. One of the major routes of transmission to man is through the consumption of contaminated foods, particularly inadequately cooked minced beef and unpasteurised milk or milk contaminated after pasteurisation. Other vehicles of O157 VTEC infection are cooked meats, meat pies, yoghurt, cheese, dry cured salami, raw vegetables, unpasteurised apple juice and water.

A study of 30 strains isolated in England and Wales from cases of haemorrhagic colitis in 1985–86 showed that only three were drug-resistant; the R-types were S, SSu and ASSu.⁴⁶ Only two of 100 strains isolated in the USA between 1983 and 1985 were drug-resistant.⁴⁷ In the period 1992–96 there has been a rise in the percentage of drug-resistant strains in both the USA and England and Wales.^{48–50} The most common R-type reported is SSuT but multiple resistance is rare. In addition to North America and Britain there have been reports of drug-resistant O157 VTEC from Japan and Italy.^{51–52} Outbreaks of O157 VTEC infection have been caused by drug-resistant strains.^{49, 50, 53} There have been very few reports of drug resistance in O157 VTEC of bovine origin.^{50–51}

7.7.2 LEP studies

The results of testing O157 VTEC strains of human origin for resistance to antimicrobial agents are shown in Table 7.8. Strains isolated from animals and raw foods have also been examined and the results are shown in Tables 7.9 and 7.10.

TABLE 7.8
O157 VTEC from humans in England and Wales

Year	Total	DR Per cent	MR Per cent
1992	470	10	1
1993	385	15	3
1994	411	20	3
1995	792	22	0.5
1996	660	18	1

TABLE 7.9
O157 VTEC from animals

Year	Total ¹	DR Per cent	MR Per cent
1992	80	6	0
1993	98	1	0
1994	137	4	0
1995	274	16	0
1996	617	14	0.3

¹ The 1,206 animals comprised 1,165 bovines, 20 sheep and 21 other animals.

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TABLE 7.10
O157 VTEC from raw foods (mainly meats)

Year	Total	DR Per cent	MR Per cent
1992	13	0	0
1993	8	0	0
1994	18	6	0
1995	13	8	0
1996	78	6	0

In O157 VTEC strains from humans, resistance to at least one drug has increased significantly since 1992 but multiply-resistant strains remain rare. The most frequent R-type was SSuT and this accounted for over 50 per cent of the drug-resistant strains in 1995 and 1996; other common R-types were SSu and SuT. Drug resistance was predominantly associated with O157 VTEC of phage type 2 over 80 per cent of the drug-resistant strains in 1995 and 1996 were of this phage type. In the O157 VTEC isolated from animals and raw foods the most common R-types were SSuT, accounting for about half of the drug-resistant strains, and also SSu and SuT. Only two of 1,165 strains from cattle were multiresistant.

7.7.3 Conclusions

Multiple drug resistance in O157 VTEC is very rare, whether from humans, human food or food animals. However there has been an increase in the incidence of resistance to some antibiotics, particularly streptomycin, sulphonamides and tetracyclines.

7.8 Conclusions

The conclusions drawn from the evidence presented in this memorandum are given again below. They are numbered according to the sections from which they were taken.

3. For salmonellas

- Multiple drug resistance is now prevalent in the epidemiologically important zoonotic serotypes *S. typhimurium*, *S. hadar* and *S. virchow*.
- Since 1990 there has been an epidemic of multiresistant *S. typhimurium* DT 104 in bovine animals and the organism is now established in other food animals including poultry. Multiresistant *S. typhimurium* DT 104 has been transmitted through the food chain to humans.
- The use of fluoroquinolones and trimethoprim in food animals has contributed to the development of resistance to these antibiotics in zoonotic salmonellas.

4. For campylobacters

- Human isolates of *C. jejuni* and *C. coli* are constitutively resistant to trimethoprim. The majority of isolates are also resistant to one or more additional drugs with a high proportion resistant to ciprofloxacin. Isolates from poultry also have a high incidence of ciprofloxacin resistance although information is very limited.
- Studies in the Netherlands have demonstrated an association between the use of enrofloxacin in poultry and the emergence of ciprofloxacin-resistant campylobacters in poultry and humans.

5. Drug resistance, other than to ampicillin, is a rare phenomenon in *Y. enterocolitica* from humans or foods.

6. With the exception of resistance to the cephalosporins, nalidixic acid and polymyxin, resistance to other drugs is rare in *Listeria* spp. However, high level ciprofloxacin resistance has been found in the UK in a few strains from humans and from food.

7. Multiple drug resistance in O157 VTEC is very rare, whether from humans, human food or food animals. However there has been an increase in the incidence of resistance to some antibiotics, particularly streptomycin, sulphonamides and tetracyclines.

7.9 References

1. Threlfall E. J., Ward L. R., Rowe B., Robins-Browne R. Acquisition of resistance by *Salmonella typhi* in vivo: the importance of plasmid characterisation. *Lancet* 1982 i: 740.
2. Rowe B., Threlfall E. J. Drug resistance in gram negative aerobic bacilli. *British Medical Bulletin* 1984; 40: 68-76.

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[Continued

3. Wray C, Davies R. H. A veterinary view of salmonella in food animals. *PHLS Microbiol Digest* 1996, 13: 44-48.
4. Anon. Report of the joint committee on the use of antibiotics in animal husbandry and veterinary medicine. London: HMSO, 1969.
5. Anon. Report of the expert group on animal feedingstuffs. London, HMSO, 1972.
6. Veterinary Products Committee. VPC 92 (36), 1992.
7. Anderson E. S. Drug resistance in *Salmonella typhimurium* and its implications. *BMJ* 1968; iii: 333-39.
8. Threlfall E. J., Ward L. R., Rowe, B. Epidemic spread of a chloramphenicol-resistant strain of *Salmonella typhimurium* phage type 204 in bovine animals in Britain. *Vet Rec* 1978; 103: 438-40.
9. Threlfall E. J., Ward L. R., Rowe B. The spread of multiresistant strains of *Salmonella typhimurium* phage type 204 and 193 in Britain. *BMJ* 1978; 6143: 997-8.
10. Threlfall E. J., Ward L. R., Ashley A. S., Rowe, B. Plasmid-encoded trimethoprim resistance in multiresistant epidemic *Salmonella typhimurium* phage types 204 and 193 in Britain. *BMJ* 1980; 1: 1210-11.
11. Threlfall E. J., Rowe B., Ferguson J. L., Ward L. R. Increasing evidence of resistance to gentamicin and related amino-glycosides in *Salmonella typhimurium* phage type 204c in England Wales and Scotland. *Vet Rec* 1985, 117: 355-57.
12. Threlfall E. J., Rowe B., Ferguson J. L., Ward L. R. Characterisation of plasmids conferring resistance to gentamicin and apramycin in strains of *Salmonella typhimurium* phage type 204c isolated in Britain. *J Hyg* 1986; 97: 419-26.
13. Ward L. R., Threlfall E. J., Rowe B. Multiple drug resistance in salmonellas isolated from humans in England and Wales: a comparison of 1981 with 1988. *J Clin Path* 1990; 43: 563-66.
14. Threlfall E. J., Rowe B., Ward L. R. Recent changes in the occurrence of antibiotic resistance in *Salmonella* isolated in England and Wales. *PHLS Microbiol Digest* 1992, 9: 69-71.
15. Threlfall E. J., Rowe B., Ward L. R. A comparison of multiple drug resistance in salmonellas from humans and food animals in England and Wales, 1981 and 1990. *Epidemiol Infect* 1993; 111: 189-97.
16. Frost J A, Threlfall, E J and Rowe, B (1995) Antibiotic resistance in salmonellas from humans in England and Wales: the situation in 1994. *PHLS Microbiology Digest*; 12: 131-33.
17. Threlfall E J, Frost J A, Ward L R, Rowe B Epidemic in cattle of *S. typhimurium* DT 104 with chromosomally-integrated multiple drug resistance. *Veterinary Record* 1994; 134: 577.
18. Wall P G, Morgan D, Lamden K, Ryan M, Griffin M, Threlfall E J, Ward L R and Rowe, B. A case-control study of infection with an epidemic strain of multi-resistant *Salmonella typhimurium* DT 104 in England and Wales. *Comm Disease Report* 1994; 4: R130-35.
19. Wall P G, Morgan D, Lamden K, Griffin M, Threlfall E J, Ward L R, Rowe B. Transmission of multi-resistant *Salmonella typhimurium* from cattle to man. *Veterinary Record* 1995; 136: 591-92.
20. Anon (1993) *Salmonella* in Animal and Poultry Production 1992. Ministry of Agriculture, Fisheries and Food, Welsh Office Agriculture Department, Department of Agriculture and Fisheries for Scotland. 1993.
21. Ridley A M, Punia P, Ward, L R, Rowe B, Threlfall E J. Plasmid characterisation and pulsed field electrophoretic analysis demonstrate that ampicillin-resistant strains of *Salmonella enteritidis* phage type 6a are derived from *Salm. enteritidis* phage type 4. *J Appl Bacteriol* 1996; 81: 613-18.
22. Anon. Animal Salmonellosis. 1984 Annual Summaries. Ministry of Agriculture, Fisheries and Food, Welsh Office Agriculture Department, Department of Agriculture and Fisheries for Scotland. 1995.
23. Nichols G L, de Louvois J. The microbiological quality of raw sausages sold in the UK. *PHLS Microbiol Digest* 1995; 12: 236-42.
24. Threlfall E J, Frost J A, Ward L R, Rowe B. Increasing spectrum of resistance in multi-resistant *Salmonella typhimurium*. *Lancet* 1996; 347: 1053-54.
25. Threlfall E J, Hall MLM, Rowe B. *Salmonella* bacteraemia in England and Wales, 1981-90. *J Clin Path* 1992; 45: 34-36.
26. Gaunt P N, Piddock LJV J Ciprofloxacin resistant campylobacter spp in humans: an epidemiology study. *Antimicrob Chemother* 1996; 37: 747-57.
27. Hawtin P, Cowden J C. Unpublished data.

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[Continued

28. Bowler ICJW, Conor M, Leasing MPA, Day D. Quinolone resistance and *Campylobacter* spp. J Antimicrob Chemother. 1996; 38: 315.
29. Report of the Chief Veterinary Officer, Animal Health 1995. HMSO 1996.
30. Endtz H P, Ruijs G J, van Klingeren B, Jansen W H, van der Reyden T & Mouton R P. Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. J Antimicrob Chemother 1991; 27, 199-208.
31. Garcia-Rodriguez J A, Fresnadillo M J, Garcia MIG *et al.* Multicentre Spanish study of ciprofloxacin susceptibility in Gram-negative bacteria. Eur J Clin Microbiol Infect Dis 1995; 14; 456-459.
32. Gomez-Garces J L, Cogollos R and Alos J I Susceptibilities of fluoroquinolone-resistant strains of *Campylobacter jejuni* to 11 oral antimicrobial agents. Antimicrob Ag Chemother 1995 39; 542-544.
33. Reina J, Ros M J, Fernandez-Baca VF J Resistance to erythromycin in fluoroquinolone-resistant *Campylobacter jejuni* strains isolated from human faeces. Antimicrob Chemoth 1995; 35; 351-352.
34. Toma S, Deidrick V R Isolation of *Yersinia enterocolitica* from swine. J Clin Microbiol 1975, 2: 478-481.
35. Mair N S, Fox E *Yersiniosis*: lab diagnosis, clinical features, epidemiology. PHLS, London, 1986.
36. Lyons M M, Prentice M B, Cope D, Swann R A. Antimicrobial susceptibility of pathogenic *Yersinia enterocolitica* strains in the British Isles. Une T, Maruyama T, Tsubokura M (eds): Current Investigations of the Microbiology of *Yersiniae*. Contrib Microbiol Immunol. Basel, Karger 1991, 12: 251-254.
37. Pham J N, Bell S M, Lanzarone J Y M. Biotype and antibiotic sensitivity of 100 clinical isolates of *Yersinia enterocolitica*. J Antimicrob Chemother. 1991, 28: 13-18.
38. Cover T L, *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*. Infections of the Intestinal Tract. 1995 Ch 55 811-823 Eds Blaser MJ, Smith PD, Ravdin Jin Greenberg HB, Guerrant RL. Ravens Press N York.
39. MacGowan A P. Listeriosis—the therapeutic options. J Antimicrob Chemoth 1990; 26: 721-20.
40. Poyart-Salmeron C, Carlier C, *et al.* Transferable plasmid-mediated antibiotic resistance in *Listeria monocytogenes*. Lancet 1990; 335: 1422-6.
41. Hadorn K, Hächler H, *et al.* 1993 Genetic characterisation of plasmid encoded multiple antibiotic resistance in a strain of *Listeria monocytogenes* causing endocarditis. Eur J Clin Microbio 1993; 12: 928-37.
42. Riviera L, Dubini F, Bellotti M G. *Listeria monocytogenes* infections: The organism, its pathogenicity and antimicrobial drugs susceptibility. Microbiologica 1993; 16: 189-204.
43. Poyart-Salmeron C, Trieu-Cuot P, *et al.* Genetic basis of tetracycline resistance in clinical isolates of *Listeria monocytogenes*. Antimicrob Agents Chemoth 1992; 36: 463-6.
44. Johnson A P, McLauchlin J, Shah S, Warner M. Antimicrobial susceptibility of *Listeria* isolated from 515 cases of human listeriosis in the UK between 1990 and 1995. Med Microbiol Lett. 1996 5: 1-7.
45. MacGowan A P, Holt HA, *et al.* In vitro antimicrobial susceptibility of *Listeria monocytogenes* isolated in the UK and other *Listeria* species. Eur J Clin Microbiol Infect Dis 1990; 9: 767-70.
46. Smith H R, Rowe B, Gross R J, Fry N K, Scotland S M. Haemorrhagic colitis and Vero cytotoxin-producing *Escherichia coli* in England and Wales. Lancet 1987; i: 1062-65.
47. Bopp C A, Greene K D, Downes FP *et al.* Unusual Verotoxin-producing *Escherichia coli* associated with hemorrhagic colitis. J Clin Microbiol 1987; 25: 1486-89.
48. Kim H H, Samadpour M, Grimm L, *et al.* Characteristics of antibiotic-resistant *Escherichia coli* O157: H7 in Washington State, 1984-91. J Infect Dis 1994; 170: 1606-9.
49. Thomas A, Cheasty T, Frost J A, *et al.* Vero cytotoxin-producing *Escherichia coli*, particularly serogroup O157, associated with human infections in England and Wales: 1992-94. Epidemiol Infect 1996; 117: 1-10.
50. Willshaw G A, Cheasty T, Frost J A, Threlfall E J, Rowe B. Antimicrobial resistance of O157 VTEC in England and Wales. Notiziario dell' Istituto Superiore di Sanità 1996; 9: No. 11 (Suppl. 3) 3-4.
51. Faring C, Goglio A, Conedera G, Minelli F, Caprioli A. Antimicrobial susceptibility of *Escherichia coli* O157 and other enterohaemorrhagic *Escherichia coli* isolates in Italy. Eur J Infect Dis 1996; 15: 351-53.
52. Tarr P I, Kim H H. Trends in antibiotic resistance of *E. coli* O157. Notiziario dell' Istituto Superiore di Sanità 1996; 9: No. 3 (Suppl. 1) 4.
53. Swerdlow D L, Woodruff B A, Brady R C, *et al.* A waterborne outbreak in Missouri of *Escherichia coli* O157:H7 associated with bloody diarrhoea and death. Ann Intern Med 1992; 117: 812-19.

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Addendum

Details of antimicrobial resistance in *Salmonella typhi*, the cause of typhoid fever, and the *Shigella* spp that cause dysentery were not included in the main part of this submission.

Table 7.11 shows the percentage resistance to chloramphenicol, still one of the main drugs for the treatment of typhoid world-wide, in isolates of *S. typhi* from patients in the UK during the past 20 years. Tables 7.12 and 7.13 show the incidence of antimicrobial resistance in *Shigella* spp in studies conducted during various periods from 1974 to 1996.

TABLE 7.11

Isolations of chloramphenicol-resistant S. typhi in the UK, 1978–96

	Years	Studied	Chloramphenicol-resistant ¹
1978–85	2,345	6	(0.3)
1986–89	790	12	(1.5)
1990	248	50	(20)
1991	226	48	(21)
1992	204	49	(24)
1993	194	49	(25)
1994	259	94	(36)
1995	291	100	(34)
1996	210	52	(25)

Notes:

¹ MIC: >32 mg/L.

Percentages in parentheses.

Source: Data from Laboratory of Enteric Pathogens.

TABLE 7.12

Incidence of drug resistance in Shigella dysenteriae, Sh. flexneri, Sh. boydii and Sh. sonnei (subgroups a-d) from humans in England and Wales

Subgroup	A, B, C			D
	<i>Sh. dysenteriae</i>	<i>Sh. flexneri</i> , <i>Sh. boydii</i>		<i>Sh. sonnei</i>
Year	¹ 1974–78	² 1979–83	1995–96	1995–96
Studied	2,370	2,753	1,524	1,733
Per cent MR	33	44	73	45

MR: multiresistant (= resistant to four or more antimicrobials).

¹Gross *et al.* 1981.²Gross *et al.* 1984.

TABLE 7.13

Resistance to individual microbials

Antimicrobial	Sh. dysenteriae, Sh. flexneri, Sh. boydii			Sh. sonnei
	¹ 1974–78 (n=2370)	² 1979–83 (n=2753)	1995–96 (n=1524)	1996 (n=1733)
Ampicillin	12	42	65	42
Chloramphenicol	12	41	61	2
Gentamicin	0.1	0.5	0.1	0.2
Kanamycin	2	2	0.5	0.1
Streptomycin	58	72	84	57
Sulphonamides	76	76	70	59
Tetracyclines	36	61	79	44
Trimethoprim	0.3	6	64	53
Furazolidone	1	>0.1	0.5	0.1
Nalidixic acid	>0.1	0.1	0.5	0.6
Ciprofloxacin	NT	NT	0.2	0.5

¹ Gross *et al.* 1981.

² Gross *et al.* 1984. NT, not tested.

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8. RESISTANCE OF GONOCOCCI TO ANTIBIOTICS

Gonococci have shown a marked ability to develop resistance to antibacterial agents. Host environmental and microbe factors contribute.

8.1 *The Organism*

Gonococci show a considerable degree of genetic heterogeneity with a probably unique level of ability to acquire DNA from other gonococci and from related species, to the extent that they are regarded as essentially non-clonal populations (O'Rourke and Stevens 1993, Maynard-Smith *et al* 1993). This ability permits the species to evolve rapidly in the face of any selection pressure, including that of the deployment of an antibiotic.

The use of sulphonamides was invariably successful in the treatment of gonorrhoea on the introduction of these drugs in 1937 (Dees and Colston 1937), however by 1944 these agents had become almost invariably ineffective (Campbell 1944). With the introduction of other antibiotics development of resistance has not been so rapid or so widespread, but a similar evolution is occurring.

8.2 *The Host*

Persons contracting sexually transmitted diseases throughout the world tend to be unconcerned about their personal health, and to exhibit poor compliance with prescribed drug regimes. They show a marked reluctance to return to treatment centres after initial visits, to the extent that "one shot" treatment (i.e., single dose therapy) is favoured by most GUM practitioners. These regimens achieve blood and tissue levels of antibiotics which are only just adequate to kill the infecting organisms, and any small change in the organisms' resistance will allow them to survive and spread, soon replacing the more sensitive strains in the population being treated by this particular means. This has led to the prescription of ever increasing doses of the penicillins so that now in the UK the maximum possible achievable dose of amoxycillin which can be given as a single dose (3.5g) is administered together with an excretion-blocking agent (probenecid). The deployment of "one shot" therapy will also preclude the possibility of sharing a course of oral antibiotics with a sexual partner. This is another reason advanced for the use of this stratagem.

Sharing a single course of oral antibiotics between an infected couple is a commonly encountered practice when such agents are prescribed. This again leads to achievement of inadequate antibiotic levels and again favours the survival and spread of strains of marginally increased resistance.

8.3 *National Antibiotic Control Policies*

In other parts of the world where antibiotics are available without prescription it is common practice to purchase very small quantities of these drugs for self treatment—with the same result of selection of resistant strains due to the achievement of inadequate blood and tissue levels, while some sex workers will take antibiotics almost continuously to prevent infection—again tending to select resistant strains.

8.4 *Availability of Alternative Antibiotics*

It has proved possible to reverse trends in increased resistance if treatment regimes are deployed which give no advantage to resistant mutants. This was first demonstrated by Morton (1963) who reduced levels of less susceptible strains (>0.25 mg/l) from 32 per cent in 1959 to 6.7 per cent in 1961 by doubling the dose of penicillin he prescribed. Similarly availability of alternative antibiotics used for situations where resistance to penicillin was likely dramatically reduced the incidence of PPNG (*vide infra*) encountered in the UK during the 1980s, when third generation cephalosporins, spectinomycin and latterly ciprofloxacin were used. These drugs are expensive and not available in developing countries.

The results of differing levels of selection pressures occurring around the world have revealed themselves in the rapid emergence of high levels of significantly resistant gonococci in the developing world, with slower increases in the UK and other developed countries. European countries with less developed antibiotic control policies (e.g., Spain) have experienced higher resistance rates than those in countries such as the UK where better control is maintained.

Changes in resistance to penicillin were originally noted by Reyn in Copenhagen (Reyn, Korner and Benzon 1958) who found strains some 20 times less sensitive than the most resistant encountered in 1944. In South East Asia and Africa the increasing resistance continued to advance rapidly so that by 1969 decreased sensitivity levels (with MIC's of up to 0.1 mg/l for penicillin) were detected in 77 per cent of gonococci isolated in the Phillipines by Keys, Halverson and Clarke (1969), with 18 per cent showing an MIC of >0.5 mg/l, whereas in the UK and Norway only 35 per cent of strains had MIC's exceeding 0.1 mg/l and MIC's exceeding 1 mg/l were rare indeed (Seth, Kolator and Wilkinson 1979).

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These changes were the result of changes to the genes on the chromosome of the gonococci, and levels of resistance of up to 2 mg/l (and occasionally beyond) occurred. In the UK strains with these levels of resistance are still only encountered at rates of between 1 and 5 per cent. These last are not susceptible to single-dose penicillin therapy. Strains with sensitivities between 0.1–0.9 mg/l remain treatable (just) with single-shot therapy and are showing an inexorable rise in proportion (see Figure) as the proportion of fully sensitive strains with MIC's below 0.1 mg/l fall reciprocally. These resistances tend to occur in association with moderate levels of resistance to other antibiotics—especially to tetracycline and erythromycin.

In the developing world levels of chromosomal resistance are now so high that frequently they will represent all strains that do not show a plasmid borne resistance (*vide infra*). For commentary see Lind (1990).

In 1976 ability to produce penicillinase was first detected in gonococci in strains deriving from the Far East (Ashford, Golash and Hemming 1976) and from West Africa (Phillips 1976). The locality of origin of these strains (PPNG) is obscure but they probably arose in the Phillipines in early 1976 in an environment of uncontrolled and heavy ampicillin usage. The ability to produce penicillinase is plasmid-mediated, and PPNG's soon spread throughout the world. Levels in the developing world rapidly reached very high levels, but spread within the UK and the Western Hemisphere was slower and deployment of alternative antibiotics not available to poorer countries has enabled the rise to be contained and even significantly reduced. Thus numbers in the UK peaked at 1,223 in 1983 and have fallen since then. Fewer than 200 strains were detected in 1993.

It has become clear that whereas originally plasmids were restricted to certain phenotypes of gonococci, as PPNGs spread around the globe their plasmids also spread within the gonococcal population.

Strains of gonococci bearing plasmid-mediated resistance to tetracycline were first reported by Knapp *et al* in 1987. These strains remain relatively uncommon in the UK but isolations from travellers indicate high levels elsewhere in the world.

Ciprofloxacin has recently become recognised as a very effective agent for the treatment of penicillin-resistant organisms, and is now used for this purpose in the UK. Unfortunately it is also being used widely in other areas of the world and this is resulting in a gradual increase in the MIC of UK gonococci and an increase in the proportion of resistant strains being encountered here (see Figure).

Current drug susceptibility patterns in the UK, and those in Sweden and in similar countries must be viewed in a different context from those of the USA and these again must be differentiated from those of the developing world. Differences between the last two groups reflect differences in populations of gonococci circulating in these countries resulting from differing Public Health provisions, etc., but incidents in countries such as Sweden, where STD control is now so efficient that the majority of infections are imported from the developing world, reflect resistance rates of those countries and high levels of resistances are being encountered as a consequence. In the UK where significant reductions in GC rates have been achieved, but where many endemic strains still circulate, resistance levels are lower and do reflect the success (or otherwise) of local policies. Figures in the USA are less good reflecting worse control of local infections.

Appended figures reveal the extent of the fall in numbers of gonorrhoeal infections in the UK and Sweden and elsewhere. These dramatic falls will also affect the relative proportions of minority populations of resistant microbes and percentage figures should therefore be interpreted with this in mind. As overall numbers fall so a minority population which survives (or is imported from afar) will increase in relative proportion.

Figures include:

1. Total numbers of gonococcal isolates in England and Wales over past decades.
2. Total numbers of gonococcal isolates in Sweden.
3. Total numbers of gonococcal isolates in USA.
4. Total numbers of gonococcal isolates for USA, Sweden and Germany.

Trends of antibiotic resistance in the UK since 1988 have been analysed by the GRU and are appended as Figures and Tables. These have been derived from two sources:

1. Resistance patterns of all gonococci isolated in Avon have been assessed. These show the whole picture for a defined area of the provinces in the UK including urban and rural populations and reveal a relatively low incidence of resistance, but with a steady diminution of the proportion of the most sensitive strains to penicillin which are being replaced by less sensitive ones, and increases in the very small numbers of frankly resistant organisms. They also show a worrying arrival of small but increasing numbers of ciprofloxacin resistant organisms.

2. Resistance patterns for strains sent to the GRU from around the country. These are assessed separately. These strains will have been selected for their resistance by referring laboratories and represent an uncontrolled sample of the resistant strains circulating (or imported) into the country. Changes in numbers can suggest trends but figures must be treated with caution. Nevertheless study of these figures reveals trends in variations in the

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levels of antimicrobial resistance which are regarded as highly informative. These show significant increases in both number and MIC of ciprofloxacin resistant gonococci (CRNG); and increase in chromosomally mediated penicillin resistance (CRMNG) from 65 to 213 isolates pa; falling incidence of PPNG strains with a commensurate rise in numbers of combined PPNG and tetracycline resistant gonococci (TRNG); and reveal a dearth of strains resistant to spectinomycin.

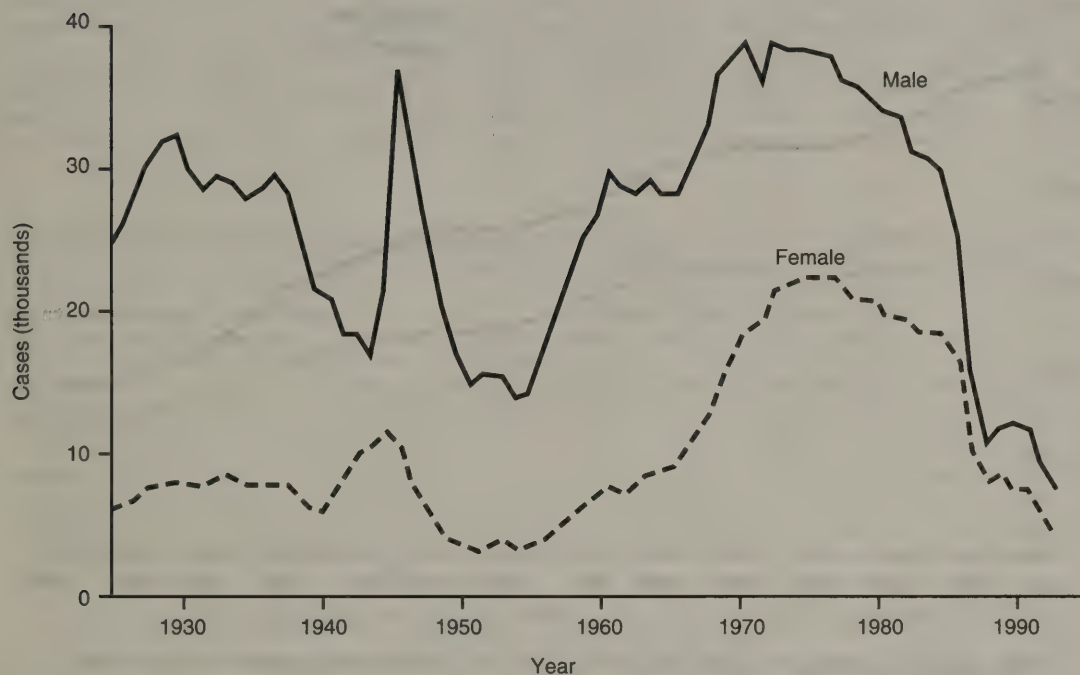
From the above commentary the reader will see that in the UK gonococcal antibiotic resistance is rising very slowly as a result of the success of imported strains surviving in our population and as a result of selection of less sensitive strains by inadequate dosing necessitated by single shot treatments, but that the availability of alternative antibiotics such as ciprofloxacin has enabled us to contain to low levels the emergence of frankly resistant organisms. In the developing world the situation is far less satisfactory with very high levels of resistance engendered by lack of alternative antibiotics and misuse of available antibiotics. Many of the resistant strains encountered in the UK (but by no means all) result from importation from such sources. This problem is far more apparent in Sweden. The situation in the United States of America, in which "ghetto" populations have disproportionately high levels of sexually transmitted diseases, control is less good than in the UK but is significantly better than that experienced in the developing world.

References

- O'Rourke M and Stevens E. Genetic structure of *Neisseria gonorrhoeae* populations: a non-clonal pathogen. *J Gen Microbiol* 1993; 139: 2643-2611.
- Maynard-Smith J, Smith NH, O'Rourke M and Spratt B G. How clonal are bacteria? *Proc Natl Acad Sci USA* 1993; 90: 4384-4388.
- Morton RS. Epidemiology of Gonorrhoea. A departure from the typical incidence picture. *Br J Vener Dis* 1963; 39: 105-108.
- Lind I. Epidimiology of Antibiotic Resistant *Neisseria Gonorrhoeae* in Industrial and Developing Countries. *Scand J Infect Dis* 1990; 69: 77-82.
- Dees J E and Colston J A C use of sulfanilimide in gonococci infections: preliminary report. *JAMA* 1937; 108: 1855-1858.
- Campbell D J. Gonorrhoea in North Africa and Central Mediterranean. *Br Med J* 1944; 2: 44.
- Reyn A, Korner B and Bentzon M W. 1958. Effects of penicillin, streptomycin and tetracycline on *N. gonorrhoeae* isolated in 1944 and 1957. *Br J Vener Dis* 1958;34:227-239.
- Keys T F, Halverston C W and Clarke E J. Single-dose treatment of gonorrhoea with selected antibiotic agents. *JAMA* 1969; 210: 857-861.
- Seth A D, Kolator B and Wilkinson A E. Sensitivity of *Neissereia gonorrhoeae* to antibiotics in London 1976-78. *Br J Vener Dis* 1979; 55: 325-328.
- Philips I. β -Lactamase-producing penicillin-resistant gonococcus. *Lancet* 1976; 2: 656-657. Ashford W A, Golash R G, and Hemming V G. Penicillnase-producing *Neisseria gonorrhoeae*. *Lancet* 1976; 2: 657-658.

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**Gonorrhoea - cases seen at STD clinics
England and Wales 1925 - 1993****Annual incidence of gonorrhoea in Sweden**

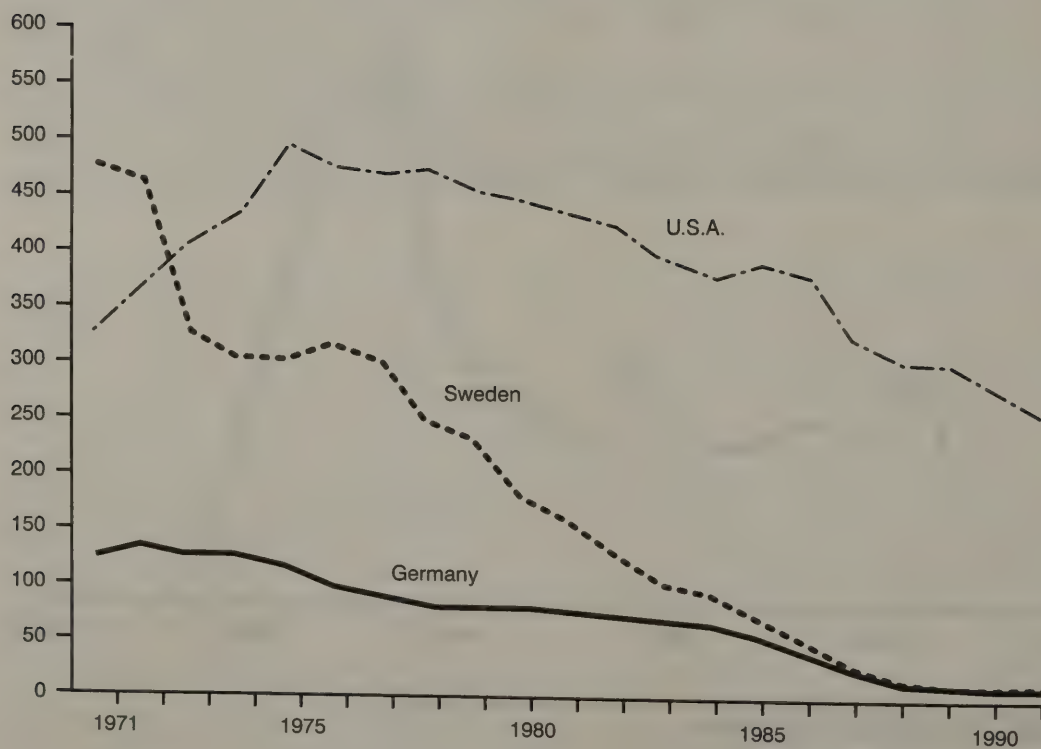
From Cronberg S, The rise and fall of sexually transmitted diseases in Sweden. Med 1993. 69 184-186. Used with permission.

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Gonorrhoea - by sex, United States, 1981-1994

In 1994, the rate of gonorrhoea among men continued to decline, among women it increased from 147.1 per 100,000 in 1993 to 153.7

Gonorrhoea cases per 100,000 population in the United States of America, Sweden and the Federal Republic of Germany, 1971-1991

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Susceptibility to penicillin of all strains of Neisseria gonorrhoeae isolated in the County of Avon 1988–1996

Resistance Category (MIC Range, mg/l)	Penicillinase Phenotype	Number of strains (per cent of total)								
		1988	1989	1990	1991	1992	1993	1994	1995	1996
Sensitive (<0.1)	—	281 (55)	214 (38)	274 (43)	183 (32)	70 (16)	114 (36)	59 (18)	50 (17)	31 (11)
Intermediate (0.1–1)	—	202 (40)	335 (60)	339 (53)	370 (65)	363 (81)	191 (61)	256 (76)	201 (68)	227 (77)
	—	13 (2.6)	4 (0.7)	8 (1.3)	6 (1.0)	2 (0.5)	7 (2.2)	7 (2.1)	8 (2.7)	15 (5.1)
Resistant (>1)	1	11 (2.2)	6 (1.1)	15 (2.4)	14 (2.4)	11 (2.5)	3 (1.0)	13 (3.9)	38 (13)	22 (7.5)
Total		507	559	636	573	446	315	335	297	295

Susceptibility to ciprofloxacin, by penicillinase phenotype, of all strains of Neisseria gonorrhoeae isolated in the County of Avon 1988–1996

Resistance Category (MIC Range mg/l)	Penicillinase phenotype	Number of strains (per cent of total)								
		1988	1989	1990	1991	1992	1993	1994	1995	1996
Sensitive (<0.05)	—	496 (98.8)	553 (98.9)	621 (97.6)	559 (97.6)	433 (97)	309 (89)	321 (95.8)	258 (86.9)	270 (91.5)
	+	11 (2.2)	6 (1.1)	15 (2.4)	14 (2.4)	11 (2.5)	3 (1.0)	13 (3.9)	36 (12.1)	17 (5.8)
Intermediate (0.05–0.9)	—	—	—	—	—	2 (0.5)	3 (1.0)	—	1 (0.3)	1 (0.3)
	+	—	—	—	—	—	—	—	1 (0.3)	3 (1.0)
Resistant (≥1)	—	—	—	—	—	—	—	1 (0.3)	—	2 (0.7)
	+	—	—	—	—	—	—	—	1 (0.3)	2 (0.7)

Susceptibility to spectinomycin, by penicillinase phenotype, of all strains of Neisseria gonorrhoeae received by the Gonococcus Reference Unit 1988–1996

Resistance Category (MIC Range, mg/l)	Penicillinase Phenotype	Number of strains (per cent of total)								
		1988	1989	1990	1991	1992	1993	1994	1995	1996
Sensitive (<128)	—	928 (85)	993 (82)	1,673 (88)	1,542 (85)	1,381 (83)	1,044 (85)	961 (85)	1,190 (84)	1,802 (89)
	+	152 (14)	214 (18)	229 (12)	280 (15)	279 (17)	176 (14)	176 (15)	219 (16)	164 (11)
Resistant (≥ 128)	—	2 (0.2)	—	—	—	—	2 (0.2)	—	1 (0.1)	—
	+	4 (0.4)	—	—	—	—	—	—	—	—

9. ANTIBIOTIC SUSCEPTIBILITY OF CLINICAL ISOLATES OF NEISSERIA MENINGITIDIS IN ENGLAND AND WALES

9.1 Introduction

The MRU performs susceptibility testing using a limited range of antibiotics on clinical meningococcal isolates sent for characterisation. These tests are done to supplement epidemiological information rather than to inform individual patient management since this has invariably been done by the submitting laboratory.

The antibiotics tested are benzylpenicillin, which has been and remains a mainstay of therapy, along with rifampicin and ciprofloxacin which are the major agents used currently for carriage eradication in close contacts, often referred to as “chemoprophylaxis”. Sulphonamide susceptibility has also been determined over a long period. These results are of more epidemiological than clinical relevance.

9.2 Penicillin

Meningococci resistant to benzylpenicillin have not yet been identified among isolates from England and Wales, however several such strains have been reported in the literature, initially in South Africa and most recently from Spain. Monitoring therefore remains vital.

Inconsistency in use of terminology with regard to penicillin susceptibility is a major problem. Organisms with MICs of < 0.1mg/l are highly susceptible to penicillin. Those with MICs between 0.1 and 1.28 mg/l have been and continue to be variously described. The terms “relatively resistant”, “moderately susceptible” or “having reduced penicillin susceptibility” are used synonymously. Infections with strains having MICs in this range would be expected to respond favourably to benzylpenicillin at doses currently recommended in the British National Formulary and also to cefotaxime and ceftriaxone which are increasingly being used as first line treatments.

The MRU has determined penicillin MIC of clinical strains submitted to the laboratory since 1984. During that time the proportion of strains with reduced susceptibility has varied from < 1 per cent in 1985–86 to nearly 14 per cent in 1995–96. The most recent data for 1996–97 is that 10 per cent strains fall into this category. (See Figure 1 attached.) The upward trend in the geometric mean penicillin MIC seen until 1995–96 was slowed in 1996–97. (See Figure 2.) The number of isolates with MIC = 1.28 mg/l has never exceeded three in any one year and in most years there have been none. No strains with higher MICs have ever been found. All strains are tested for β -lactamase production and none have been found.

In general, group C isolates have higher mean MICs than group B isolates. The mean MIC levels of group B and C2a strains have risen in parallel. Those of C2b isolates are currently notably higher. This was observed in strains from Spain in the early 1990s and has been a feature of C2b isolates in England and Wales since 1995. (See Figure 3.) The incidence of disease caused by C2b strains has *not* increased in recent years, indeed the trend has been to lower numbers in both proportional and absolute terms.

9.3 *Other β -lactam antibiotics*

There have been no reports of isolates suspected of being resistant to third generation cephalosporins or to any of the new β -lactam antibiotics. The MRU is currently assessing the MICs of these antibiotic groups to isolates identified as having “reduced penicillin susceptibility”.

9.4 *Rifampicin*

Rifampicin is the most widely used agent for eradication of meningococcal carriage among contacts of meningococcal disease cases. Resistance is defined as having an MIC > 5 mg/l. The number of resistant clinical isolates remains very low comprising no more than 0.4 per cent isolates in any given year. Such resistant strains are not infrequently traced back to contact by the case with individuals who have recently received rifampicin chemoprophylaxis. This highlights the importance of using such intervention in a targeted fashion and sparingly.

9.5 *Ciprofloxacin*

In age groups where ciprofloxacin can be safely prescribed, particularly when large numbers of individuals are involved, it is used as a single dose treatment for carriage eradication. The ciprofloxacin MIC for clinical strains has been monitored since 1993. All strains examined to date have been susceptible to low levels (<0.1 mg/l) of ciprofloxacin. For the overwhelming majority (90 per cent+) of strains the MIC is the modal value (0.01 mg/l) or lower.

9.6 *Sulphonamides*

Sulphonamide resistance among meningococci is defined as organisms with MIC = >10 mg/l. Isolates divide distinctly into susceptible and resistant strains. The proportion of resistant strains has fallen steadily from 40 per cent in 1986–88 to 25 per cent in 1995–97. Use of the group of antibiotics for carriage eradication in the UK has ceased because of the high proportion of resistant strains and the relatively high incidence of side effects which they cause. The usefulness of sulphonamide resistance as a marker for important organisms from the ET-5 clone has diminished as the proportion of cases caused by these strains has fallen.

9.7 *European collaboration*

A recent meeting of representatives from the European meningococcal reference laboratories—the European Monitoring Group on Meningococci (EMGM) has agreed as one of its projects an assessment of MIC methodology used by the various laboratories. This is to be followed by a re-audit of susceptibility testing as follow-up to an exercise performed two years earlier. The aim is to identify best practice and to encourage its widespread adoption. The PHLS MRU is leading this assessment and the audit.

Kaczmarek, E B Meningococcal disease in England and Wales: 1995, CDR Review, 1997, 7, R55–59.

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[Continued

Figure 1
Proportion meningococcal disease case isolates highly susceptible to penicillin
(MIC <0.1mg/l) by year (July 1985-June 1997)

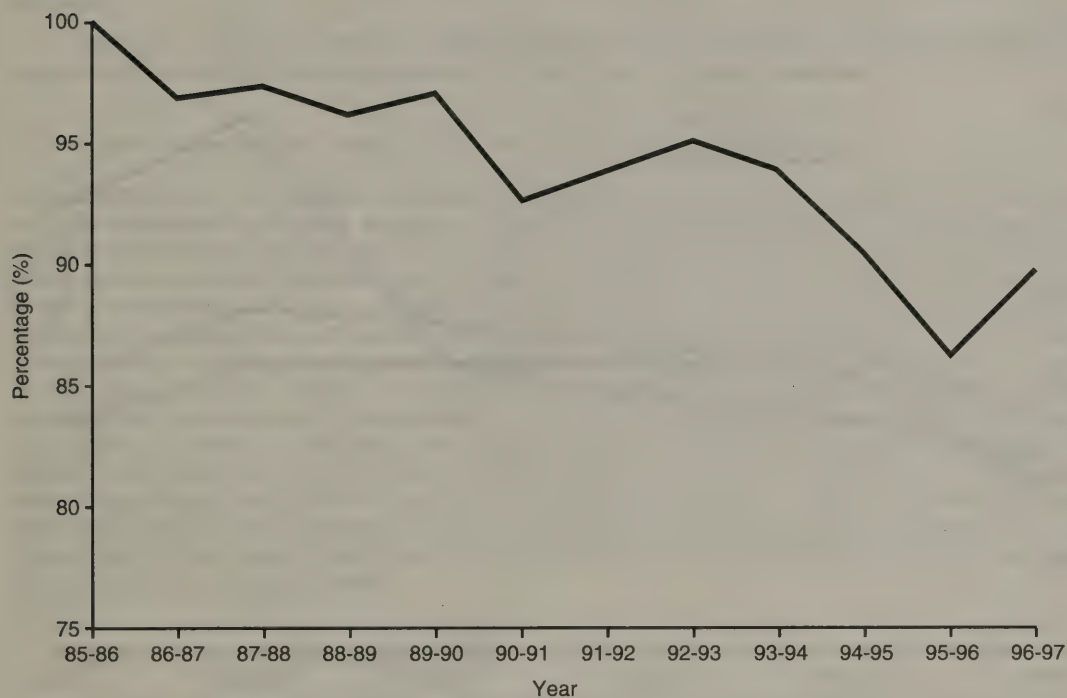
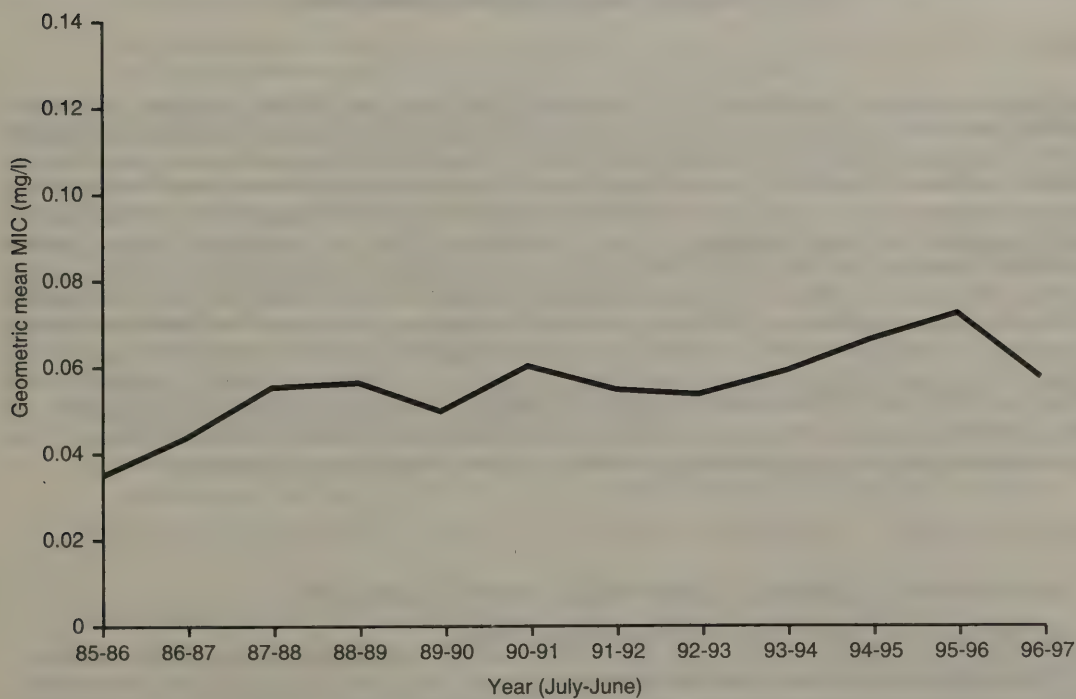


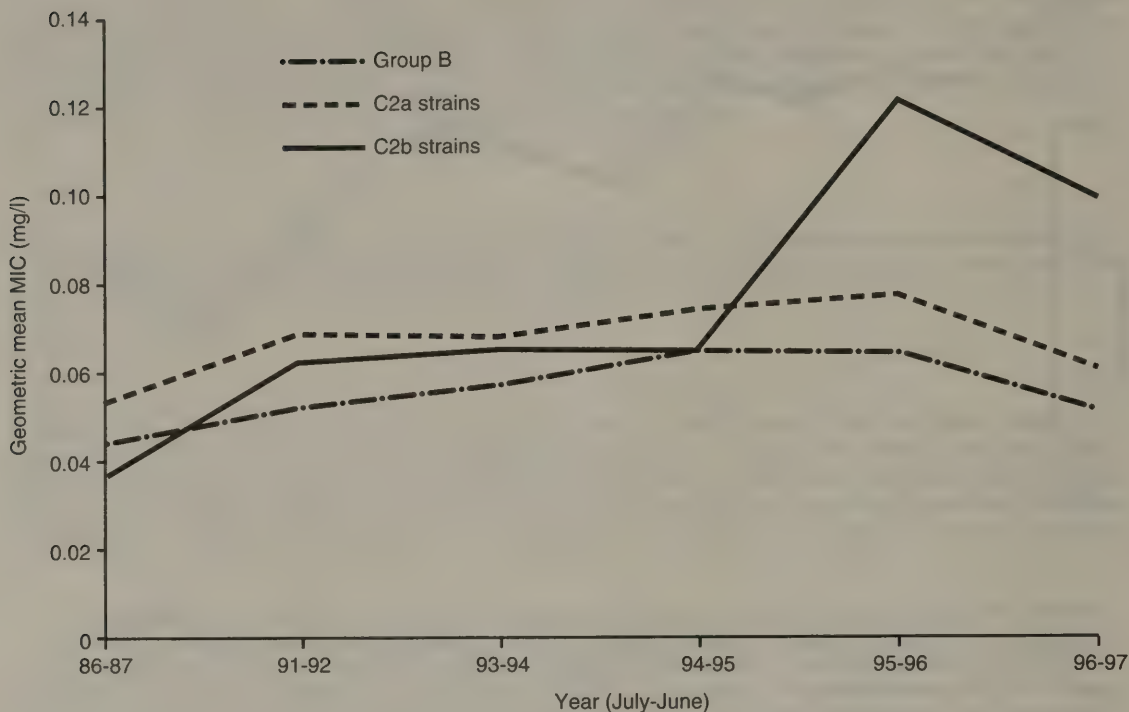
Figure 2
All meningococcal clinical isolates July 1985-June 1997
Geometric mean penicillin MIC



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Figure 3
Meningococcal clinical isolates - Geometric mean penicillin MIC
Group B, C2a and C2b strains - selected years 1986-97



Memorandum by Dr Alasdair P MacGowan, Chairman, British Society for Antimicrobial Chemotherapy (BSAC) Working Party on Resistance Surveillance

SUMMARY

Antimicrobial resistance surveillance is the systematic, deliberate and planned collection of bacteria susceptibility data with analysis and conclusions which is then disseminated. A good surveillance programme will establish the present amount of resistance, monitor new resistances occurring and observe general trends. Surveillance does not in itself have a direct impact on resistance but is central to the process of combating antimicrobial resistance. This is because the information collected is of use in planning and monitoring schemes to control resistance. Information technology is vital to this process. There are a number of different methods of surveillance depending upon the specific problem area to be addressed. At present the best quality data on antimicrobial resistance is produced via pharmaceutically sponsored studies performed by private companies, the NHS or university departments. Such data collection is, however, short term. The PHLS also collects resistance data. The British Society for Antimicrobial Chemotherapy has recently set up a Working Party on Resistance Surveillance. It has proposed a multi level approach to surveillance in the UK. Discussions have started with the PHLS as to how surveillance in the UK can be improved by a collaborative arrangement. In addition the BSAC is actively seeking partnerships with the pharmaceutical industry and the Wellcome Trust, and has a proactive approach to implementing its concepts of surveillance during 1998 and beyond.

STRUCTURE OF SUBMISSION

This submission on *Surveillance of Antimicrobial Resistance* is in eight parts:

1. The British Society for Antimicrobial Chemotherapy (BSAC)
2. What is surveillance of antimicrobial resistance?
3. What is the role of surveillance in combating antimicrobial resistance?
4. What types of antimicrobial surveillance are there?

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5. How is antimicrobial surveillance currently performed in the United Kingdom?
6. What options are available for antimicrobial surveillance in the United Kingdom?
7. The British Society for Antimicrobial Chemotherapy proposals for improved surveillance in the United Kingdom.
8. What has the British Society for Antimicrobial Chemotherapy achieved to date and how does it plan to promote improved antimicrobial surveillance in the near future?

1. *Description of the British Society for Antimicrobial Chemotherapy (BSAC)*

The British Society for Antimicrobial Chemotherapy (BSAC) is an association with a current membership of over 600 professionals who share a common interest in antimicrobial chemotherapy. The largest group within the Society are medical microbiologists, but scientists and technicians who work in the PHLS, the NHS or universities are also well represented. In addition the Society has a significant number of members who work in the pharmaceutical industry. As well as members in the UK, the Society has members in Europe and elsewhere. The Society aims to have a positive impact on antimicrobial developments and usage through its working parties, educational activities and research grants. The working parties have published recommendations on laboratory techniques, criteria for antimicrobial susceptibility, anti infective development, education of prescribers and students, medical management of a number of infections and over the counter anti infectives. A working party is currently collaborating with others to develop an improved antibacterial resistance surveillance system in the British Isles. Through its Education Committee the Society sponsors a number of activities to increase awareness of anti infective issues, mainly among prescribers. The Grants Committee distributes over £100,000 per annum on anti infective research. The Society also produces a medical journal, the *Journal of Antimicrobial Chemotherapy*, which since its inception in the early 1970s has gained an international reputation for the quality of the work published.

2. *What is surveillance of antimicrobial resistance?*

Surveillance is the systematic, deliberate and planned collection of data; analysis of the data with conclusions and feedback of the information to those who provided it and others. In the context of antimicrobial resistance it is the collection of data on bacterial susceptibility to a specific antibiotic or antibiotics and assessment of how that changes over time or between different places. Bacterial susceptibility for the purposes of surveillance can be thought of in two ways;

- (a) the proportion of bacteria that are resistant to a drug; that is infection due to such a resistant bacteria is unlikely to respond to therapy with the drug;
- (b) the occurrence of bacteria with reduced susceptibility to the drug compared to the normal population of bacteria, whether or not this will affect the outcome of treatment.

It is sometimes the case that reduced susceptibility to a drug occurs and then resistance with clinical failure occurs some years later—such a picture is seen with penicillin resistant pneumococci.

There are often very marked differences in bacterial resistance between geographical locations whether it be between countries, cities or within hospitals between wards.

The way antimicrobial surveillance is organised depends on the particular questions those organising it wish to answer but a good antimicrobial surveillance system should;

- (i) establish resistance data now for clinically relevant pathogens using robust, reproducible, adequately controlled and respected laboratory tests;
- (ii) monitor the emergence of new resistances which presage new problems, for example—vancomycin resistance in *Enterococcus* or *Staphylococcus* species;
- (iii) monitor changes in less dramatic resistances, for example—quinolone resistance in *Escherichia coli*, cephalosporin resistance in *Klebsiella* sp or methicillin resistance in *Staphylococcus aureus*;
- (iv) monitor general trends in resistance to a wide range of antimicrobials.

3. *What is the role of antimicrobial surveillance in combating antimicrobial resistance?*

Surveillance of antimicrobial resistance will not have a direct impact on the incidence of resistance but it is central to the whole process of combating antimicrobial resistance. The data from a surveillance programme will show those areas where resistance is greatest and by continued surveillance over time enable the impact of control measures such as improving human and veterinary antimicrobial use, prevention of infection or improved laboratory diagnosis to be assessed.

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[Continued

Surveillance to be conducted in the near future will help determine priorities for action depending on the degrees of resistance in different bacteria or in different locations. In the longer term, surveillance data can be correlated with human antimicrobial use, veterinary antimicrobial use, infection control strategies or the ways in which healthcare is delivered to help ascertain the major influences on development of resistance. Such correlations could be developed by use of observational or interventional studies. Good information technology is important in these processes.

4. *What types of antimicrobial surveillance are there?*

There are many types of antimicrobial surveillance depending on what those involved wish to achieve. For example, many clinical diagnostic laboratories regularly analyse the results of sensitivity tests performed for therapeutic purposes in order to help inform hospital antibiotic formulary decisions as well as the development of local infection treatment protocols. Such data often goes back many years. In contrast pharmaceutical companies perform widescale national or international surveillance, often over a relatively short period of time, to help in making commercial decisions about antimicrobial marketing and new antimicrobial development (for example, the SmithKline Beecham sponsored Alexander Project). At present no body regularly analyses and publishes data in the UK to inform public policy decision making about resistance.

The important considerations in surveillance include

- (a) *local, regional, national and international*—as rates of resistance vary, national surveillance should include a wide and representative number of areas where data is collected.
- (b) *community, nursing homes, district general hospitals and teaching hospitals*—Most patients who are treated with antibiotics are treated in the community by their general practitioners, therefore antibacterial resistance will affect most people outside hospital. Nursing homes and hospitals, however, have greater rates of resistance but this affects a small number of patients. Collection of data should include all these elements.
- (c) *laboratory techniques*—there are generally two laboratory techniques used to test susceptibility.

- (i) *methods of susceptibility testing*

- qualitative methods such as the agar disc diffusion test*

- these tests are very commonly used in diagnostic laboratories in the UK and allow bacteria to be categorised as sensitive, intermediate or resistant in their susceptibility to an antibiotic.

- quantitative methods*

- these methods are based on the determination of a minimum inhibitory concentration (MIC). This is a numeric value and allows for a more detailed analysis than disc tests, of the data generated. It also allows bacteria to be categorised as susceptible or resistant by the use of breakpoints. Breakpoints are at present defined in the UK by the BSAC. MIC methods are not commonly used in UK diagnostic microbiology laboratories for clinical purpose. They are almost always used in specifically designed surveillance studies rather than routine laboratory data. However their performance requires more time, expertise and resources than disc tests.

- (ii) *quality control*

- Quality control is simplest when one laboratory in a surveillance programme tests all the strains against all the antibiotics. Strains are usually sent to this single laboratory from various geographical locations. If, on the other hand, each laboratory tests its own strains then procedures have to be put in place to ensure all the laboratories get comparable results—this is called External Quality Assessment (EQA). This is generally more time consuming, expensive and difficult to manage than a programme where a central laboratory does all the tests.

- (iii) *source of the isolates tested*

- Most, if not all, surveillance systems use bacteria isolated from specimens sent by doctors to clinical laboratories for analysis. The factors which go into the decision to send a specimen are complex and may change over time. Therefore the bacteria used in surveillance may not be coming from the same type of infection or severity of infection as time goes on or as you move from hospital to hospital or country to country. This type of collection introduces bias into the data generated. It may be that the best way to develop surveillance systems is to collect specimens specifically for the purpose but this would add greatly to the time and effort required to do surveillance. When using diagnostic laboratory isolates information such as age, sex, location and type of infection also need to be collected. This is aided by good information technology.

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[Continued

(iv) *typing of resistant bacteria*

If it is known that 1 in 10 strains of bacteria of a certain species are resistant to an antibiotic it is important to know if the strains making up the resistant population are just the same strain which has infected many people (clonal spread) or if all the strains are different. Typing helps to do this. For example, at present in the UK methicillin resistance in *S. aureus* is becoming increasingly common which is due to the spread of two different clones of bacteria known as EMRSA-15 or EMRSA-16.

- (d) *frequency of surveillance*—the frequency is dictated by the information required. Usually in national surveillance yearly collection and analysis is sufficient. For local surveillance to guide prescribing practices more frequent monitoring is more useful.
- (e) *calculating rates of resistance*—rates of resistance are usually calculated by dividing the number of resistant strains discovered by the total number of bacteria of that species tested. Alternative methods use the number of patients infected.

5. *How is surveillance performed at present in the UK?*

On a national level surveillance is conducted in two ways, through the PHLS network and via pharmaceutically sponsored studies. The data collected by the PHLS is based on routine laboratory testing which may vary between laboratories and the existing external quality assurance is not exacting enough for epidemiological purposes. The PHLS at present does not regularly return analysis of the sensitivity data it collects on a routine basis to those who provide it. Much of the data published in medical journals derives from pharmaceutically sponsored studies. The best example in recent times is SmithKline Beecham's worldwide surveillance study on respiratory pathogens—the Alexander project. This project followed the model of collection of isolates by many laboratories but testing using quantitative methods in only one. The central laboratory used is located in London. In the UK in the last 2 years Bayer, Hoechst Marion Roussel, Rhone Poulenc Rorer and Zeneca have all performed surveillance studies. Although the pharmaceutical industry in conjunction with private companies, NHS and university laboratories has put considerable effort into producing good quality surveillance data so far, this has not resulted in an ongoing surveillance programme. The government, the NHS Research & Development programme and charities have not funded large scale surveillance schemes.

At a local level, many laboratories use their existing laboratory computer systems to monitor resistance.

6. *What options are available for antimicrobial surveillance in the UK?*

In 1997 the BSAC set up a working party to provide input into improving antimicrobial surveillance in the UK. In its first report to the BSAC Council—"Towards a British Surveillance Scheme" (Appendix A)—the working party concluded that a scheme should include the capacity to:

1. identify and estimate problems
2. collect data in a standard way
3. disseminate important information
4. advise and evaluate programmes of control of
 - (i) antibiotic use
 - (ii) infection control
5. generate hypotheses
6. trigger investigations
7. assist in direction of new pharmaceutical developments

In order to do this effectively it is important to develop links with other European countries as well as on a worldwide basis. Hence the use of the WHONET software package to collect epidemiological information is of considerable importance. In order to augment the existing UK systems several models are available.

(a) *Comprehensive*

All microbiology laboratories report all antibiotic sensitivity tests. This model would detect all resistances but is likely to be too expensive, very difficult to implement, require a much higher level of external quality assurance than is in place at present and is likely to be unmanageable.

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[Continued]

(b) *Comprehensive but targeted*

Data is collected in one or more potentially important areas, for example pathogens causing hospital acquired infection. This system may be more manageable but risks missing important events outside the area of focus.

(c) *Spotter Systems*

A small number of Departments send data on one pathogen or pathogenic group to a central collection/analysis point. This is a manageable system, a high degree of quality assurance is possible but there is a danger of missing important events.

(d) *Centralised/Specialised Central Reference Laboratory*

This laboratory would receive problem isolates for study. Such a model is affordable and gives detailed answers on mechanisms of resistance but does not provide good quality epidemiological information. In many ways the PHLS Antibiotic Reference Unit fills this role for England and Wales.

7. *British Society for Antimicrobial Chemotherapy (BSAC) proposals for improved surveillance in the UK*

The BSAC paper "Towards a British Surveillance Scheme" (Appendix A) has proposed a pragmatic approach to surveillance for the British Isles. Its elements are:

1. The scheme will have a management board consisting of four members from BSAC and four from PHLS—this model was originally proposed by the PHLS.
2. Using the new standard BSAC disc method (qualitative results) which will be ready in late 1997/early 1998, laboratories in the PHL network plus NHS or university laboratories using the method will feedback results of routine tests to the Central Epidemiology Unit (most likely Communicable Disease Surveillance Centre but regional collation of data or analysis of data by others is not excluded). The PHLS will take a lead role here.
3. Laboratories feeding back routine disc test results will participate in an extra, more demanding level of External Quality Assessment than that already in place through the UK National External Quality Assessment Scheme (UK NEQAS). The External Quality Assurance may be conducted by UK NEQAS or others.
4. Specialist laboratories will be set up by the BSAC with commercial partners to perform epidemiological studies based on qualitative methodology (MIC tests on specific pathogen groups over a minimum of five years—for example respiratory pathogens, skin and soft tissue pathogens or urinary tract pathogens). This will allow resistance patterns from the larger qualitative disc test derived database to be validated by more accurate testing methods. In addition laboratories will retain isolates for typing and study of resistance mechanisms as appropriate. The BSAC will take a lead role here.

8. *What the BSAC has accomplished and is planning in the near future to promote antimicrobial resistance surveillance*

The BSAC is in contact with the following bodies about furtherance of surveillance.

- *PHLS* to hear the PHLS view on the BSAC proposals for surveillance; as a first step to set up the proposed management board and subsequently, in partnership, improve the quality of UK surveillance.
- *Scottish Antimicrobial Resistance Surveillance Group (SARS) and Scottish Office* to develop a collaborative approach to surveillance in Scotland so that data for the UK can be viewed as a whole.
- *WHO* to use WHONET software as an integral part of data collection and ensure UK data is available internationally.
- *The Wellcome Trust* to help promote the setting up of a high quality surveillance programme within the UK as well as analysis of resistance data and correlation with factors which may be causative.

Within the Society

(a) *The Working Party on Antibacterial Susceptibility Testing*

(Chairman: Professor R. Wise) has almost completed development of the new BSAC standardised disc testing method—this will form the cornerstone of qualitative surveillance by PHLS and other laboratories in the future.

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(b) *The Working Party on Resistance Surveillance*

(Chairman: Dr A P MacGowan)

- (i) produced a paper of surveillance "Towards a British Surveillance Scheme" (Appendix A)
- (ii) produced an initial protocol for qualitative (MIC) data collection on respiratory pathogens to start in October 1998 (Appendix B—not printed).

(c) *The BSAC Council* has approved "Towards a British Surveillance Scheme" so that discussions with the PHLS and others can commence.

Within the near future the Society hopes to:

1. start agreeing proposals for antimicrobial surveillance with the PHLS (late 1997);
2. meet and discuss surveillance with those interested in Scotland (late 1997);
3. discuss surveillance further with The Wellcome Trust (late 1997/early 1998);
4. have a demonstration and copies of WHONET software available in the UK (Late 1997);
5. agree a final protocol for respiratory tract pathogen surveillance by quantitative methods and allocate funding (early/mid 1998);
6. approach pharmaceutical partners about support of the Society's efforts in surveillance (late 1997/early 1998).

Acknowledgements

I would like to thank my fellow members of the BSAC Working Party on Resistance Surveillance and Dr I M Gould (Aberdeen), Dr R G Masterton (Edinburgh) and Dr J R Stephenson (Wellcome Trust) for a number of useful discussions on resistance surveillance over the last year.

In addition I would also like to thank my work colleagues—Professor D S Reeves, Dr L O White and Mrs K E Bowker who helped with the preparation of this submission.

The membership of the Working Party is as follows:

Alasdair MacGowan (Chairman)—Southmead Hospital, Bristol
Consultant Medical Microbiologist

Derek Brown—PHLS, Cambridge
Clinical Scientist

Jeff Edwards—Zeneca Pharmaceuticals, Macclesfield
Manager: Anti infectives
Development and Technical Support Group

David Livermore—Central PHLS, London
Head: Antibiotics Unit

Tony White—SmithKline Beecham, Harlow
Director: Scientific and Technical
Product Support

Richard Wise—City Hospital, Birmingham
Consultant Medical Microbiologist
Professor of Medical Microbiology
President: BSAC

APPENDIX A**BSAC Working Party on Antimicrobial Resistance****TOWARDS A BRITISH SURVEILLANCE SCHEME**

The terms of reference of the Working Party are to:

- consider ways to enhance the surveillance of antimicrobial resistance in the British Isles;
- co-operate with others, notably the Public Health Laboratory Service, to achieve this;
- report back to the BSAC Council with potential solutions and their costs;

Surveillance of Antimicrobial Resistance is essential to ensure appropriate use of antimicrobials, optimal clinical outcomes in infection management, priority is given to infection control, direct resource utilisation and to guide the development of new anti infectives or other strategies in infection therapy.

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[Continued

To date there are no comprehensive schemes in the United Kingdom—a piecemeal approach exists and comprises:

1. individual microbiology laboratories monitoring certain pathogens or pathogen groups—often supported by the pharmaceutical industry;
2. individual laboratories monitoring their own resistance rates over many years—this has become increasingly easy with the development of IT systems in laboratories;
3. a small number of laboratories involved in wider studies. Some funded through Government such as the PHLS nosocomial study, or others through industry such as EPIIC and others;
4. the PHLS network reporting antimicrobial susceptibilities based on a wide variety of methodologies on routine isolates for central collation;

As a more comprehensive scheme is envisaged it is important to define what will be required. A surveillance scheme can:

- (a) establish baseline resistance data in clinically relevant pathogens;
- (b) monitor emergence of new events which presage new problems—for example vancomycin resistance in *Enterococcus* species;
- (c) monitor changes in less dramatic resistances—for example quinolone resistance in *E. coli* or methicillin resistance in *S. aureus*;
- (d) monitor general trends in resistance to a wide range of antimicrobials.

The scheme can only be justified if it can influence future events and to this end the early involvement of those likely to be involved in actions derived from the surveillance process is necessary. Hence appropriate and timely feedback of collected data is essential.

The scheme should include the capacity to:

1. identify and estimate problems;
2. collect data in a standard way;
3. disseminate important information;
4. advise and evaluate programmes of control of i) antibiotic use and ii) infection control;
5. generate hypotheses;
6. trigger investigations;
7. assist in direction of new pharmaceutical developments.

In order to do this effectively it is important to develop links with other European countries as well as on a worldwide basis. Use of the WHONET software package to collect epidemiological information will ensure data from the UK can be made available internationally. Equal and open access to the data must form an integral part of the system.

A number of organisations in Europe are at present developing surveillance programmes, some of which are governmental such as the Swedish National System while others derive funds from the EU and industry, such as European Network of Antibiotic Resistance and Epidemiology (ENARE). The exact form of collaboration with these groups and others has yet to be defined. The most important priority is to augment the existing UK surveillance systems. Several models have been considered:

- (A) *Comprehensive*: all microbiology laboratories report all antibiograms. This model would catch all events but is likely to be expensive, very difficult to implement, require a much higher level of QC than is at present in place and is unlikely to be manageable.
- (B) *Comprehensive but targeted*: just collect data in one or more potentially important area, for example nosocomial infection. This system may be more manageable but risks missing important events outside the area of focus.
- (C) *Spotter systems*: a small number of Departments sending data on one pathogen or group to a central collection/analysis point. This is a manageable system, high QC possible but there is a greater danger of missing important events.
- (D) *Centralised/specialised central reference laboratory*: This laboratory would receive problem isolates for study, such as a model is affordable and gives detailed answers on mechanisms of resistance but

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does not provide good quality epidemiological information. In many ways of the PHLS Antibiotic Reference Unit fills this role.

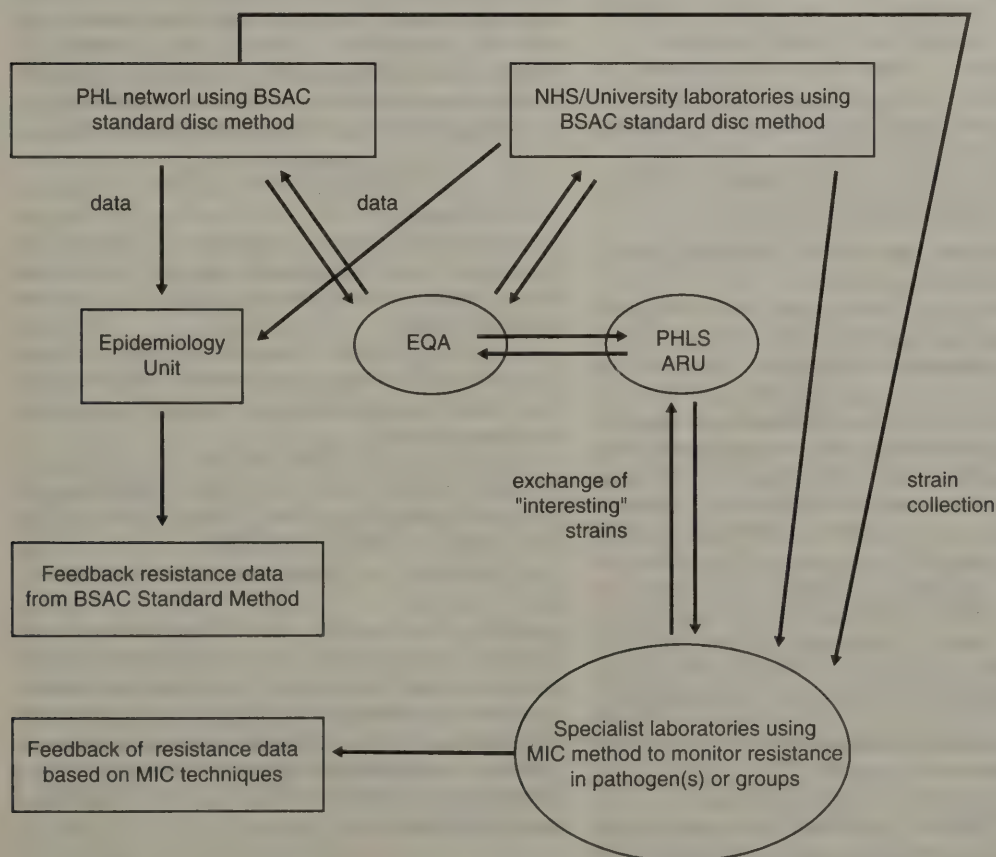
(E) *Pragmatic*: a mixture of the above.

The Working Party propose the following mechanism of surveillance which is pragmatic one.

- (i) The scheme will have a management board consisting of four members from BSAC and four from the PHLS—this model was proposed by Professor B I Duerden.
- (ii) Using the standard BSAC disc method to be introduced in late 1997/early 1998, laboratories in the PHL network plus other NHS laboratories will feedback results of routine tests to the central epidemiology unit—this is most likely to be CDSC but regional collation of data or analysis by others is not excluded. PHLS will take a lead role here.
- (iii) Laboratories feeding back routine disc test results will participate in an extra, more demanding, level of EQA than that already in place through UK NEQAS. This EQA may be conducted by UK NEQAS or others.
- (iv) Specialist laboratories will be set by the BSAC with commercial partners to perform MIC based epidemiology studies on specific pathogen groups—for example respiratory pathogens, *Ps aeruginosa*, skin soft tissue isolates, etc. This will allow resistance patterns from the larger disc test derived database to be validated using a more exact methodology.

This will require some financial commitment from the Society, perhaps in the order of £30,000–50,000 pa for 3–5 years.

The flow diagram below summarises these proposals:



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[Continued]

Examination of witnesses

DR ALASDAIR MACGOWAN, Department of Medical Microbiology, Southmead Hospital, Bristol, and Chairman of the Working Party on Antimicrobial Resistance Surveillance of the British Society for Antimicrobial Chemotherapy; PROFESSOR A PERCIVAL, former President, British Society for Antimicrobial Chemotherapy; PROFESSOR BRIAN DUERDEN, Deputy Director (Programmes), Public Health Laboratory Service; PROFESSOR PETER BORRIELLO, Director, Central Public Health Laboratory, Public Health Laboratory Service; DR CHRISTOPHER BARTLETT, Director, Communicable Disease Surveillance Centre, Public Health Laboratory Service; and DR DAVID LIVERMORE, Head of the Antibiotic Reference Unit, Public Health Laboratory Service, were called in and examined.

Chairman

69. Good morning. Thank you for coming. Some of us have met some of you before. Would you like to introduce yourselves to the others, and say what particular part of the spectrum of activities you, yourself, cover.

(*Professor Duerden*) I am Professor Brian Duerden. I am Deputy Director of the Public Health Laboratory Service.

(*Dr Bartlett*) I am Christopher Bartlett. I am an epidemiologist and I am Director of the PHLS Communicable Disease Surveillance Centre, which is responsible for surveillance of communicable diseases in England and Wales.

(*Dr Livermore*) I am David Livermore and I am Head of the Antibiotic Reference Unit of the Public Health Laboratory Service.

(*Professor Borriello*) I am Peter Borriello, Director of the Central Public Health Laboratory.

(*Dr MacGowan*) I am Alasdair MacGowan, a Consultant Microbiologist at Southmead Hospital in Bristol. I am the Chairman of the BSAC Working Party on Resistance Surveillance.

(*Professor Percival*) I am Professor Percival, Professor of Clinical Bacteriology, Liverpool.

70. Is there any statement that you wish to make before we start the questioning?

(*Professor Duerden*) I presented in the PHLS's submission the data that we have relating to the resistance to antibiotics in a range of micro-organisms and the problems that causes in their infections. We hope that shows that it is a **multi-faceted problem**. It is not one single problem with a single answer. We have given examples that are in tuberculosis, being a community problem and of international concern, through resistance in Staph aureus and Gram-negative bacilli and enterococci that are essentially problems in hospital; and problems spreading out into the community; problems with Streptococcus pneumoniae which is very much a community problem. In all of these, resistance has been shown to increase and is posing a potential threat to the treatment of infection.

71. What are the data which you do not collect, and the **limitations of the data** which you have? In particular, how selective is the information at your command, and how can you obtain true or meaningful denominator data? Are you constrained by lack of resources? How could the situation be improved?

(*Professor Duerden*) We did recognise that this was a huge question and we can fill it out in a written submission if you so wish. We do not ask for routine

data on resistance patterns on all bacteria, or a range of bacteria at the moment. We restrict ourselves to specific problem organisms and to isolates from invasive infections: in other words, blood-stream isolates and cerebrospinal fluid isolates, where we do ask routinely for resistance data. In other areas we either do special studies, such as with the pneumococci, where we ask for all isolates to be submitted over a short period of time and analyse their behaviour, or we collect data through the special reference laboratories, such as for MRSA, for vancomycin-resistant enterococci and the gonococci. These are special studies and reference services. The data we do not collect reflect perhaps the wider pattern of resistance or susceptibility in the community at large, where we do not necessarily get the specimens into the laboratories. We have not conducted special surveys through the PHLS for those. We do not collect data that match antibiotic resistance patterns to antibiotic prescribing. Clearly the pressure for resistance must be the amount of antibiotic prescribed both in human medicine and veterinary medicine. We are not in a position at this stage to match up those.

Baroness Masham of Ilton

72. Why not?

(*Professor Duerden*) In that we do not have the links to the prescribing data directly that would allow us to do that. It is something we feel is important that should be done.

(*Professor Percival*) There are not any data apart from Wales. We cannot get data when we ask for it, the amount of antibiotic used nationally, the very important efficacy.

(*Dr MacGowan*) There are also data in parts of Scotland where you can relate prescribing in geographical areas, particularly around Dundee. They have a well developed system there.

73. So that is something that should be improved on?

(*Professor Percival*) Yes. The concept that antibiotic resistance is related somehow to the amount of use is critical because if it is not true then we have no chance of controlling it. That is why I think it is important. Although everybody believes that, the evidence to support it and to demonstrate it in a scientifically acceptable way is largely lacking. I mean world-wide.

Lord Rea

74. Would you be going on to talk about the information you can get from PACT; that is, the Prescription Costs Analysis that the Prescription

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DR ALASDAIR MACGOWAN, PROFESSOR A PERCIVAL,
 PROFESSOR BRIAN DUERDEN, PROFESSOR PETER BORRIELLO,
 DR CHRISTOPHER BARTLETT and DR DAVID LIVERMORE

[Continued]

[Lord Rea Contd]

Pricing Authority does. How much is that of use to you?

(*Professor Duerden*) These are not data we have actually had ourselves; are not part of our data set.

75. They are there for us, so why can we not make use of it?

(*Professor Duerden*) I think they should be made use of. They have not been up until now.

76. Surely it is simply a question of talking to someone and it will be made available to you? Is that not possible? Has it been tried?

(*Dr Bartlett*) CDSC have not been involved in antimicrobial susceptibility surveillance with the exception of mycobacteria.¹ Of course it should be possible to look at resistance in other micro-organisms and relate the data to prescribing practice.

Lord Rea] This gives a picture of what every GP in the country is prescribing.

Lord Jenkin of Roding

77. As I understand the problem, it is that the database of resistance is incomplete and that, therefore, even if you did have at your disposal all the figures, you would not be able to make anything very much of it. Is this because you would not be able to get an exact correlation between the nature of prescribing and the growth of resistance, which, as I understand it, you are anxious to establish?

(*Dr MacGowan*) The bacteria that you use to establish resistance rates are the bacteria from the specimens that one's colleagues send to the laboratory. That process, the decision making process to send a specimen, is quite complicated in its own right. Not all patients with a specific condition will get a specimen taken. There may be differences in different doctors' approaches to that. There may be differences in hospital and community in different parts of the country. So you are quite right in saying that the data we have, based on laboratory isolates, is biased in some way. We do not know quite how it is biased. You can try and address that, of course, in a number of different ways. For example, trying to get prescribers to send specimens on all patients with a certain condition; or you could go out and try and sample the bacterial flora in healthy people, although that does not necessarily tell you what is causing the infection or resistance in those areas. Therefore, you certainly do have problems in deciding what population you are sampling. There are a few ways of approaching that.

(*Professor Percival*) Most people think there is an innate bias towards an accentuated view of resistance in this instance, because in the community general practitioners tend to send specimens either only or most often from patients who have failed treatment, and not as a primary measure before starting it. So if you wanted to get a better view of what the primary,

as it were, level of resistance is in pathogens, you would have to arrange special studies with general practitioners in order specifically to do just that.

(*Dr MacGowan*) It is further complicated by the medical condition: if you think about a condition like chronic bronchitis, where in most patients it is caused by bacterial infection; the patients, by definition, produce sputum. Therefore, you can get a specimen. However, you will not grow a pathogen from quite a lot of them. That is in contrast to, say, pneumonia where most patients do not produce a specimen which you could culture anyway. So there are not only logistical problems in getting specimens. There are actual medical problems as well. From some patients you will not get a specimen for the best reasons.

Chairman

78. Is there a possibility of you being involved in what one might call sentinel medical practices?

(*Dr MacGowan*) Absolutely.

(*Professor Duerden*) It was not mentioned specifically but we would look to use sentinel practices where there is a heightened level of sampling of their patients. So we would be looking to establish links with specific general practitioners. It has obviously to be on a national basis to get the right spread across the country.

Lord Rea

79. How far has that gone?

(*Dr MacGowan*) In the particular laboratory where I work we already have a link with a general practice surgery. That is one link, of course. We try to get the general practitioners in that surgery to send us all sputum specimens from patients with chronic bronchitis. That is part of a research study. So you can do it. Then you can look at their prescribing patterns, using their computer systems. Therefore, the answer is yes, you can do it, but you would need to do it on a bigger scale nationally.

(*Professor Duerden*) From the PHLS point of view, we are looking to establish links with general practitioners across the country, as part of a GP research initiative that we are trying to establish as part of this year's new activities.

80. Is the Royal College of GPs involved in this? Are you talking to them about trying to arrange this network?

(*Professor Duerden*) We are in touch with them because, of course, we have good links on the influenza epidemiology spotter practice approach, so there is some experience there to build upon.

Lord Walton of Detchant

81. To what extent do you believe that you are collecting information from the community, in comparison with what you are collecting from the hospital service? Obviously you are getting a lot more from the hospitals and a lot more specimens. Is there

¹ Note from witness: In this new scheme, MYCOBNET, information is collected on treatment in patients with TB; it is planned to analyse treatment regimens in relation to acquired resistance.

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[Continued]

[Lord Walton of Detchant Contd]

any kind of numerical comparison that you can offer us at the moment?

(*Professor Duerden*) I could not offer a direct numerical comparison, except that we are certainly heavily biased from the information which is provided from hospital patients rather than general practitioners.

82. Apart from the methods that you have talked about in collaborating with general practitioners, what other techniques do you believe are needed to try to improve information about infections and organisms that are loose in the community?

(*Professor Duerden*) As well as getting material from known infections, there is the question: do you actually go out into the community with special studies to survey the organisms that are there? I believe you have some comments about that, Professor Borriello.

(*Professor Borriello*) It is quite evident from the questions and some of our answers that the problem is a very big one indeed. Of that there is no doubt. It is also quite complicated. Quite naturally, we would think within the arena of clinical practice and our own health, but the pressures on the emergence of resistance and the transfer of resistance come from many sources. One of the most popularly discussed additional sources is the use of antimicrobials in non-clinical practice. There have been some statements to the effect that up to half of all the antimicrobial usage is non-clinical. That is human clinical. This situation is difficult to deal with because if particular antibiotics are identified as a stimulus for the emergence of resistance in an antimicrobial used in clinical practice, then managing without those antimicrobials simply means they are replaced with others and we are just perpetuating the situation. There are other antimicrobials used in animal husbandry—or even more specifically **aquaculture**—which is an aspect which is rarely touched upon; with the intensive fish farming and the associated diseases due to that intensity and therefore the liberal use of antimicrobials, many of which are not specifically designed for fish. So because it is a new discipline—**aquaculture**—therefore they turn to antibiotics used in the veterinary field or even in the human clinical field. These obviously go straight into food chain and the environment through the water. So the aspects I really wanted to raise were with the complexity of those issues, some of which have been touched upon in the written documentation.

83. How much is the process of surveillance subject at the moment to **audit**, and how satisfied are you with the quality of the audit that is being conducted?

(*Dr Livermore*) The main basis of audit comes from NEQAS, the National External Quality Assurance Scheme, which involves the quality assurance part of the service sending out organisms to participating laboratories. This includes the great majority of United Kingdom clinical laboratories. These data are then collected and collated to ensure that accurate results are obtained. One can be very confident that most clinical laboratories in the United Kingdom—virtually all—can accurately identify methicillin-resistant staphylococcus, say, or a

penicillin-resistant pneumococcus. In fairness, one has to say that in all susceptibility testing there is a grey zone between fully susceptible and fully resistant; certainly in the hospital Gram-negative bacilli and with agents such as the quinolones. There are not nationally agreed definitions of resistance—indeed, not internationally agreed definitions of resistance in these cases—so it is difficult to audit performance.

84. And do any of the private laboratories participate in this quality assurance scheme?

(*Dr Livermore*) Yes.

Chairman

85. Could I ask whether there is any similar surveillance in the **animal health** field, fish farming field, of resistance?

(*Professor Percival*) Yes, my Lord Chairman. Weybridge Laboratories keep records of antibiotic resistance among salmonella isolates from animal sources. So there is a surveillance, yes. It publishes its results every year.

86. We are to receive evidence from NOAH and FEDESA. They would challenge some of the things which were said about the inter-relationship between animal feed and veterinary use and the food chain. We have heard from other witnesses that they would conclude quite a definite link.

(*Professor Duerden*) We would certainly conclude that from the salmonella data in human infections, where over the last few years with *Salmonella typhimurium* DT 104 we have seen the new emergence of resistance to trimethoprim and the quinolones. These have coincided with the introduction of those agents into veterinary use.

Lord Jenkin of Roding

87. Would you share the view that this link was not proven?

(*Professor Duerden*) We would regard it as established.

88. We have had some evidence which simply says that it is not proven.

(*Dr Livermore*) Its importance surely varies with the particular organism and antibiotic combinations. There are some where surely veterinary usage is important. *Salmonella* DT 104 has just been mentioned. *Campylobacter* could be mentioned in the same context. There are other instances, for example, pneumococci, where the link is unlikely.

(*Professor Borriello*) To a certain extent we tend to put restrictions on bacteria which they do not have themselves. There is no doubt whatsoever that the evidence is conclusive that different bacterial species view the earth as their habitat and that they do move freely between soil, animals and humans both ways, although not all. It is also proven that bacteria develop resistance to antibiotics and can transmit resistance to others of the same species or different species. Therefore, the recipe for that transmission, whether directly proven or not—and there will be different

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sides to the argument due to different interests—but the recipe undoubtedly proves that it not only can happen but does happen.

Baroness Masham of Ilton

89. Who collects the information on drug resistance in **parasites** of both humans and animals?

(*Professor Duerden*) The parasite drug resistance that we are, for example, particularly concerned about in malaria and tripanosomes, is collected by the laboratory at the London School of Hygiene and Tropical Medicine and the Tropical Diseases Hospital. Our reference laboratories are there with Professor Bradley, Dr Warhurst and Dr Chiodini. They monitor, in particular, the malaria drug resistance.

90. What about parasites of sheep, horses, pigs, and things?

(*Professor Duerden*) I do not know. That would be a veterinary responsibility to do that.

Lord Porter of Luddenham

91. You have expressed some concern obviously which must exist about the incompleteness of the database on antimicrobial resistance. Now last week we met the Association of Medical Microbiologists and they had a suggestion to counter this to some extent. We would like to know how you feel about this. They suggested that the Infectious Diseases Regulations should be extended to enforce reporting from laboratories and to make resistance notifiable in its own right. Would you favour **regulation** on these lines?

(*Professor Duerden*) We would certainly favour regulation to enforce the statutory requirement for reporting specified infections. We would link with that particular problem antibiotic areas. I do not think you could make a blanket decision that all antibiotic resistance should be reported. That would be far too broad and you would be overwhelmed with data.

92. Could you indicate what sort of organisms would be covered?

(*Professor Duerden*) We have a very brief list of the highlighted ones. Clearly it changes from time to time. These are our thoughts at the moment.

PROPOSED NOTIFIABLE RESISTANCES

Already known elsewhere

S. aureus—vancomycin

N. meningitidis—penicillin

Enterobacteriaceae (not *Proteaeae*)—carbapenems

Acinetobacter—carbapenems

Feared, not yet known elsewhere

Str. pyogenes—penicillin

Str. pneumoniae—vancomycin

Str. pneumoniae—ALL β -lactams

+ Multi-drug resistant TB—mostly tested by PHLS already

(*Dr Livermore*) Essentially the list is composed of resistant organisms which have not been found in the United Kingdom but which have been encountered elsewhere. Vancomycin-resistant *Staph aureus* is clearly top of the list, on the grounds that we have big MRSA problems, and if those MRSA also become resistant to vancomycin we are without a good systemic antibiotic. *Neisseria meningitidis* resistant to penicillin is next. Resistance has been reported abroad. Some of these reports are rather dubious. It is certainly one to be feared. Carbapenems have really been the beta-lactams of last resort against hospital Gram-negative rods, but there are increasingly scattered reports from around the world now of resistance to them; this needs to be monitored. At the bottom we have types of resistance which have not, to the best of our knowledge, been reliably reported anywhere in the world yet, but which one fears may evolve given the way bacteria seem to be cleverer often than we are. Group A streptococci could become resistant to penicillin. *Streptococcus pneumoniae* could become resistant to vancomycin or a wide range of beta-lactams. Notification of multi-drug resistance in tuberculosis is also desirable but that effectively happens anyway since susceptibility testing of TB is largely handled in-house anyway by PHLS for England and Wales. All these cases we feel should be notifiable, at least so that the reference laboratory can check it is a valid report and advise appropriately.

93. Would you envisage strong objection from the medical profession or anyone else to making these notifiable?

(*Dr Livermore*) I would not think so on the basis of that list. If one was to start making all resistance notifiable, people would be overwhelmed with the amount of information they had to submit. We would be overwhelmed with the amount that came in. This I would say is really the key list.

94. So there is no reason you see why we should not go ahead tomorrow?

(*Professor Percival*) Could I reinforce the views of my colleagues. There is no organism that is not resistant to one or other antibiotic, both in the community and in hospital. Many are resistant to quite a lot of antibiotics. Therefore, you would just get a huge morass of indigestible information. All the laboratories would be trying to do their work and would not have the time to report them. We want to report things which are valuable and useful. You would have to identify initially a very small number of new or important rare resistances.

Lord Jenkin of Roding

95. I was wondering why you have not included glycopeptide resistance in enterococci. In Professor Duerden's evidence in 4.2 and 4.3 there is a discussion of this. The words are used that if it turns out to be so the result would be "catastrophic" and I can understand that. Is this not something you would want to include?

(*Professor Duerden*) It is something which is being monitored. I would not say our list is exhaustive. We have highlighted some very key resistance markers

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there, which would be dramatic if they were to become widespread. In hospital practice, in particular, glycopeptide-resistant enterococci are important, particularly in transplant units and chemotherapy units. Whether one would want to make it nationally notifiable would need to be debated with the people working in those areas. It is a possibility. We certainly need to know more about it.¹

(*Dr Bartlett*) In addition to a limited list, it may be helpful to put in place an untoward event reporting system in which any unusual or unexpected resistance marker in any micro-organism is reported. The advantage of this is that you can identify new antimicrobial resistance events at an early stage and implement investigations to try and sort out the determinants. Untoward event reporting has been shown to be very effective in disease surveillance.

96. There would need to be extensive consultation before any definitive requirements were written into the system?

(*Dr Bartlett*) Yes.

Baroness Platt of Writtle

97. Would you describe briefly the surveillance of resistance in the parts of the United Kingdom not covered by the PHLS, which I understand is **Scotland and Ireland** and Wales. Is there sufficient comparability and co-ordination and compatibility in terms of producing national data for the whole United Kingdom?

(*Dr MacGowan*) If I can answer that for BSAC. I have had some preliminary discussions with colleagues in Scotland, where there is a Scottish Antimicrobial Resistance Surveillance Group. I do not quite know exactly what that structure is and quite how wide it is. I also happen to know from another colleague in Scotland, that the Scottish Office formed a committee recently to look at antibiotic resistance. In terms of the situation in Ireland, speaking to the President of the Irish Clinical Microbiology Association, she is not aware of any surveillance in Southern or Northern Ireland. She is not aware of what is happening in Northern Ireland, particularly on this issue. There is a problem, in terms of integration of the various national parts of the United Kingdom, as to what we should be doing.

(*Dr Bartlett*) There is one exception, which is the surveillance of resistance in *Mycobacterium tuberculosis* which causes TB. There is a system in place which is co-ordinated by the PHLS, involving the reference laboratory in Edinburgh and one in Belfast, as well as the four reference laboratories in England. There are six reference laboratories altogether. 95 per cent of all isolates are reported to the co-ordinating centre. This gives good

representative information on the current resistance in mycobacteria in the United Kingdom.

Chairman

98. This is co-ordinated by the PHLS?

(*Dr Bartlett*) Yes, it is co-ordinated by the PHLS. The other laboratories are in Edinburgh and Belfast.

(*Professor Duerden*) In your first question you suggested Wales was outside the system. PHLS covers England and Wales.

Baroness Platt of Writtle

99. But not Northern Ireland.

(*Professor Duerden*) We do need to improve the links with Scotland and Northern Ireland to get the national picture. They tend to go their own way.

100. Perhaps this would be a possibility from the point of view of IT.

(*Professor Percival*) Could I just say that the evidence is there. Sensitivity testing is a daily part of diagnostic bacteriology in all of this. The evidence is there. It could be co-ordinated better.

Lord Winston

101. Can you tell us how the findings of surveillance actually contribute to the **treatment of individual patients**, to the provision of health services, and to research; and how they alter prescribing policies?

(*Professor Percival*) All treatment is started empirically, so-called blind. It should not be blind, it should be based on probabilities. What are the likely effects of the organisms? What are their likely sensitivities? So all treatment is initiated empirically. The essential part of that is information. You must know what the predictability of the sensitivities are for the likely infecting organisms in any particular clinical infection. Then if you take a culture, you get it confirmed. It takes two days. First day, culture positive; second day, sensitivities. The more severe the infection, the more comprehensive the initial empirical treatment must be. If it is bacterial meningitis the patient can die in 24 hours, so you must have a 100 per cent cover, including rare resistant strains. If it is a minor infection, where the patient is not going to die or suffer greatly, then the cover need not be so comprehensive. In the first instance, surveillance resistance data are absolutely essential for empiric protocols—hospitals and GPs—antibiotic policies which are based on those two factors: what are the likely infecting organisms in order of commonness and severity, and what is the predictability of their sensitivities? So surveillance determines your antibiotic policy. As resistance rises, then you have to review that policy and change it. At what point you change it is arbitrary. Do you change it when the organism becomes 10 per cent or 20 per cent resistant? If it is meningitis, you change it when it is 3 per cent or 1 per cent resistant. If it is a urinary infection, maybe not until it is at 10 per cent or even 20 per

¹ Note from witness: What would be catastrophic would be transfer of this resistance to *Staph aureus*.

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cent resistant. So it is the absolute backbone of the rationalisation of antibacterial therapy.

(*Professor Duerden*) If I can give an example in the tuberculosis field because this does inform the national guidelines on that. It is very important that high quality information is spread to the clinical disciplines to develop policies in general. As regards the MYCOBNET for mycobacteria, information is provided to the committee of the British Thoracic Society, which will be issuing guidance shortly on treatment of tuberculosis.

Lord Jenkin of Roding

102. What do you regard as the **biggest threat to public health** in this field?

(*Professor Percival*) World-wide, malaria. The biggest resistance problem world-wide is malaria. It is not much of a problem for us.

103. I am still taking my malaria tablets from Africa!

(*Professor Percival*) I would say in hospitals, MRSA, which is continuing to grow in many hospitals which have not had the problem before. If vancomycin resistance appears, then that would be a very, very critical situation. Very critical indeed.

Lord Winston

104. May I come back to something you said before, Professor Percival, about **empiric therapy**. First of all, one would like to know how much pressure there is to try and reduce the minimum 48 hours to get specific sensitivities. Also, to what extent do you think empiric therapy does actually contribute to the problem of resistance?

(*Professor Percival*) Well, it does. It is partly related to another question about whether it would be wise to have nationally recommended treatment policies. When you go to the States, the States has recommended treatment protocols for different diseases, like gonorrhoea or whatever. There you have the problem that if the protocol is appropriate then it is fine. It just means that if you do not use it you can be sued. That is a problem. What happens here is that sometimes a policy gets misdirected. For example, the British Thoracic Society said some years ago that for all people with severe community acquired pneumonia you use a combination of antibiotics comprising erythromycin and a cephalosporin to cover all the various possibilities. What happens is that all of the prescribing initially in hospital is done by junior doctors, almost all. So everybody with pneumonia of any kind, severe or mild, community or hospital, gets put on these two antibiotics. Some people are now saying that that itself, that policy, has led to a tremendous increase in *Clostridium difficile* side effects. So I think it is inter-related.

Lord Jenkin of Roding

105. May I come back to what you see is the biggest threat. How likely is **VRSA**?

(*Professor Percival*) It has happened already, we are told. It is inevitable sooner or later.

(*Professor Duerden*) It has been reported from Japan and the USA and will occur here.

106. What should we do to avert that?

(*Professor Duerden*) Control the usage of glycopeptide antibiotics and vancomycin as best we can, and monitor the strains that are appearing, because the key to the staphylococcal story will be trying to prevent transmission of the infection. It is cross-infection control as well as antibiotic policies to restrict prescribing, in that order, for MRSA and VRSA.

Baroness Masham of Ilton

107. What aspects of public health **research** would you most like to see funded in this field and by whom?

(*Dr Bartlett*) What I would certainly like to see is support for the development of surveillance systems within an overall national surveillance strategy. At least there needs to be developed a consensus beyond the PHLS, working with colleagues in the NHS and academia, including clinicians and public health colleagues also. I would wish to see new systems very carefully evaluated, such as sentinel-based surveillance which was referred to earlier on. I would like to see rapid detection and identification systems for mycobacteria and other infections as well.

(*Professor Duerden*) We need to improve our research into the relationship between prescribing practice and the occurrence of resistance, which goes back to the very first question of matching up the antibiotics prescribed to the resistance patterns.

(*Professor Borriello*) It is quite evident from the evidence you have heard already that the causes are multi-factorial. Therefore, the solutions in many cases will also be multi-factorial. One has to look, as you have heard, at prescribing practices. More importantly, to have some research into what may influence prescribing practices, if indeed that is shown to drive resistance. If you determine that it does lower the emergence of resistance, you need also to know how you can influence the prescribing practice. It is not usually the easiest thing one can envisage because you are dealing with individuals. The other thing is, very briefly, that there are alternatives to the so-called classical antibiotics, as treatments and therapies for certain infections. Certainly there should be much more research into some of the newer anti-bacterial peptides and how these can be stabilised and potentially used. There need to be better controlled studies of alternative therapies. Alternative therapies should be subjected to the same sort of critical appraisal as a standard antibiotic, if they are ever to be proven to be useful and to be used. So there are alternatives, but they need to be subjected to proper scrutiny.

108. With the pressure on health authorities—if you looked at the programme last night on the Manchester Hospitals, *Panorama*—four patients in a bed in 24 hours. One can understand how MRSA can spread rather quickly. Those mattresses were not being sponged down. Should other money come in rather than just health authority money?

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(*Professor Percival*) I agree. I think more funding should be more readily available for pragmatic research into the sort of things we are discussing today. You cannot get grants because it is viewed to be intellectually inferior; not more than half a millimetre deep. Most funds these days are partly, as in all human affairs, fashion, fad and privilege. If you are not analysing the gene, or knocking off the extreme left-hand bit of a ribosome, often to no particular purpose, you do not get any funds. That is the position. I think it is in sore need of some balance. I agree with you. I go to see patients who have been in four beds in the same hospital, different wards, in the same week. How we can contain MRSA in that kind of circumstance goodness only knows. Yet there is no evidence, no study going on to assess the effect this has, the so-called triage system.

Lord Phillips of Ellesmere

109. Do not many of these suggestions which you have made depend upon the **increased rapidity** in the identification of the infective agents, so that more specific use can be made of existing treatment?

(*Professor Duerden*) To some extent, yes. We certainly do need to improve diagnosis. Microbiology is still traditionally producing results in 24 or 48 hours. New technology is allowing the possibility of improving that, but it will not replace the existing methods entirely because you can only ask specific questions of new technology, such as "Is organism A present? Is resistance marker B also present?" but it can be done although it is very expensive.

(*Dr MacGowan*) And we come back to one of the main problems when we are assessing interventions, that we are still not very certain what the correct method of surveillance is and we still have not done studies to look at surveillance and when you ask who should be looking at some of these issues related to the provision of health care, then I suppose part of the answer is the **NHS R&D Directorates** should be trying to address some of these issues and I am not sure that it does at present—again for the reasons which Professor Percival has mentioned, that it may not be seen to be very fashionable, I am afraid.

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**Memorandum by the Division of Emerging and other Communicable Diseases Surveillance and Control,
World Health Organization, Geneva, Switzerland**

1. The intense pressure exerted on microorganisms through the massive and increasing use of antimicrobial agents in man, animals and in agriculture has created a resistance problem which is rapidly moving to the forefront among public health concerns. The critical issues are that:

- Antimicrobial-resistant pathogens are emerging and spreading more rapidly than in previous decades;
- Antimicrobial resistance is a global problem, affecting developed and developing countries, and rapidly spreading between continents through international travel;
- Treatment of resistant infections is increasingly hampered either due to the prohibitive cost of existing “new generation” agents or a total lack of effective antimicrobial agents on the market;
- Antimicrobial resistance should be viewed within the context of the larger public health environment.

2. Addressing the complex problem of antimicrobial resistance requires multiple actions:

- *Surveillance* to define the extent of resistance among different pathogens and in different populations; to adjust treatment strategies and national drug policies and to measure the success of intervention strategies.
- *Education* of policy makers, prescribers, health care professionals, and the general public, to reduce overuse and misuse of antimicrobial agents.
- *Regulation* to achieve maximum availability and quality of antimicrobial agents in all the world's markets; the instigation of, and adherence to, patent laws; control of unethical promotion of antimicrobial agents.
- *Research* to develop new agents with new mechanisms of action; to study the cost implications of resistance and the cost-effectiveness of its detection; to link laboratory data on resistance to treatment outcome.
- *Public health infrastructure* to reduce the need for antimicrobial treatment by improving the health of the world populations.

WORLD HEALTH ORGANIZATION (WHO) SUPPORTS MEMBER STATES TO COMBAT RESISTANCE

3. Antimicrobial resistance and other emerging infectious public health threats were addressed in a resolution by the World Health Assembly in 1995. In order to support the response of Member States to these threats, WHO established the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC). The Antimicrobial Resistance Monitoring (ARM) programme is coordinated by EMC. In addition, antimicrobial resistance has long been a concern also for several of the specialised WHO programmes (see Appendix).

4. These programmes are represented in the Task Force on Resistance to Anti-Infective Drugs established by the Director-General to provide advice on the development of WHO policy and strategy on matters relating to diagnosis, surveillance and the rational use of antimicrobial drugs.

5. This statement, prepared by the ARM programme in collaboration with other programmes represented in the Task Force, reviews briefly the action items listed above and the activities of WHO relevant to each. Further details from individual WHO programmes are provided in the Appendix.

Surveillance

6. Surveillance alone will not control the threat of antimicrobial resistance; it provides information which must be translated into action. The information derived from surveillance should be used:

- at the local level to guide empiric treatment, identify outbreaks of resistant infections and guide hospital antimicrobial policy and control of drug costs;
- at the national level to develop policies for purchase and use of antimicrobials and reduce inappropriate drug use;
- at the global level to analyse the impact of resistance and monitor control policies, engage policy-makers, develop advocacy and education programmes, stimulate development of appropriate new drugs and update the WHO model list of essential drugs;
- by the pharmaceutical industry for registration purposes, marketing strategy and development of new agents.

7. No global surveillance system of antimicrobial resistance exists today. A few countries operate national systems coordinated by reference laboratories. Many local and some multicentre (international) surveillance systems have been initiated. Often these are sponsored in some way by the pharmaceutical industry and thus

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tend to be concentrated in countries that are commercially attractive to the industry. At present there is no repository for information about the systems that do exist nor coordination between them.

8. Existing surveillance systems are laboratory-based and depend on specimens being taken from patients, bacterial isolates grown, and antimicrobial susceptibility tested; all of which have cost implications. However, the vast majority of antimicrobial prescriptions are made empirically by general practitioners or other community health care providers.

9. The Antimicrobial Resistance (ARM) programme in EMC assists developing countries to establish national laboratory-based surveillance networks through provision of training, an external quality assurance scheme, laboratory reagents, and computer software. Local surveillance is linked to national and regional networks and feeds into an ARM global "network of networks". This global system will also contain information from existing surveillance in developed countries.

10. For some diseases such as sexually-transmitted infections and tuberculosis, which tend to be investigated and treated separately, organism-specific networks may be more appropriate. WHO sponsors the Gonococcal Antibiotic Susceptibility Programme (GASP) in the American and Western Pacific Regions of WHO (now being extended to WHO Region of South-East Asia).

11. Specialized networks also exist for monitoring drug resistance among *Mycobacterium tuberculosis* (in the Global Programme on Tuberculosis), and for leprosy (in the Action Programme for the Elimination of Leprosy) to detect any sign of resistance that could threaten the successful multidrug therapy scheme to eliminate leprosy. The results of the first four years of the WHO Global Project on Anti-tuberculosis Drug Resistance Surveillance will be published in 1997. This is a large international study on drug resistance against *M. tuberculosis* in 35 countries in all continents. For the first time, standardized, quality-controlled data obtained through a network of supranational reference laboratories and using comparable epidemiological approaches will be available.

12. With respect to malaria, a database has been established to collect information on drug resistance and to advise countries.

Education

13. There is a great need for education of the purchasers, prescribers and consumers of antimicrobials. Many prescribers obtain up-to-date information only from pharmaceutical industry by way of medical representatives, they feel under pressure to prescribe through lack of knowledge, fear of litigation, or perceived patient expectations. Physicians also need to be alerted to resistance in pathogens in other regions of the world as international travel allows one country's resistance problem to be transported to almost any other country within 24 hours. Patients would benefit from greater understanding of what antimicrobials can, and cannot cure, and the importance of compliance.

14. To counter the lack of independent information, WHO is developing *Model Prescribing Information* on infectious diseases and a *Model Formulary* giving concise information on all the drugs on the *WHO Model List of Essential Drugs*. The Antimicrobial Resistance Monitoring programme together with the Division of Drug Management and Policies and the Action Programme for Essential Drugs sponsors national policy workshops which aim to improve collaboration between decision-makers in health policy and planning so that they can develop a coherent strategy for monitoring resistance and develop policies for antimicrobial use and containment of resistance infections.

15. In addition, recommendations on choice of antimicrobials and avoidance of unnecessary treatment form part of the guidelines on disease control (acute respiratory infections, diarrhoeal diseases, malaria) and advice given to the general public. Simplified treatment schemes have been introduced to educate patients in the correct use of antimicrobials in the treatment of leprosy and tuberculosis.

Regulation

16. Licensing and import of, and commerce with, pharmaceutical preparations are in general regulated by national authorities. Where regulations are weak or absent the judgment is left to pharmacies and other pharmaceutical drug dispensers who can operate in the absence of supervision and exposed to heavy marketing pressure. WHO has developed guidelines on many aspects of regulation and is encouraging the wide dissemination and implementation of its *Ethical Criteria on Medicinal Drug Promotion*. In general, countries where antimicrobial agents are widely available without prescription suffer greater resistance problems than those where these agents are obtainable only on prescription.

Research

17. Despite the widespread use of laboratory tests to detect resistance, much less is known about the correlation between resistance demonstrated *in vitro* and outcome of treatment and research is needed. The full cost of resistance needs to be evaluated in terms of increased morbidity and mortality, prolonged hospital stay,

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increased person-to-person spread of resistant infections. Research is also needed to evaluate the cost of surveillance, detection and prevention of spread of resistant microorganisms.

18. The Special Programme for Research and Training on Tropical Diseases encourages research for new agents including antimalarials with novel mode of action, particularly drugs which modulate or reverse resistance and will ensure patient adherence to full oral regimens. The Division of Child Health and Development fosters research towards new antibiotics for treatment of acute respiratory infections and evaluates new inexpensive tests to identify clinical resistance.

19. Data gathered in the study on *M.tuberculosis* resistance will be used to evaluate the impact of the directly observed short course therapy (DOTS) on drug resistance prevalence and the impact of multidrug resistance on DOTS programmes. Studies to assess the response to standardised treatment regimens are required to better define treatment policies. Methods for detecting resistance that can be used in the clinic and in the field need to be designed.

20. Research must also be encouraged to develop new antimicrobials appropriate for the needs of the world.

Public health infrastructure

21. Efforts to build public health infrastructures to improve the general health situation of the world's populations, to reduce poverty and malnutrition and improve the prospects for disease prevention are concentrated mainly in WHO programmes other than those dealing with the acute problem of antimicrobial resistance. However, it is critical for countries to recognise that the impact of resistance in some infections (such as typhoid, dysentery, tuberculosis) can be lessened by improving the overall health of their people. Meanwhile, the increased life expectancy and "high-tech" medical interventions in many developed countries have brought with them increased risk of infection with resistant pathogens particularly in hospitals.

WHO ACTION IN COLLABORATION WITH MEMBER STATES

22. The problem of antimicrobial resistance has triggered many responses on the local, national and international level. Sharing of information and expertise and creation of partnerships to optimise use of resources and avoid duplication are essential to combat this global threat.

The ARM programme is the focal point of WHO activities aimed at reducing emergence and spread of antimicrobial resistance and it works with other WHO programmes and other partners ranging from Ministries of Health, NGOs, professional societies, and health care facilities to the pharmaceutical and diagnostics industries to:

- improve dialogue and encourage partnership in surveillance, research and education;
- advocate for more stringent regulations of marketing and sale of antimicrobial agents in all Member States;
- develop indicators to measure success of efforts to monitor and control of resistance.

Dr Rosamund Williams

Scientist

Division of Emerging and Other Communicable Diseases Surveillance and Control

WHO

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APPENDIX

WHO DIVISIONS AND PROGRAMMES WITH COMPONENTS CONCERNING ANTIMICROBIAL RESISTANCE

23. In addition to the Antimicrobial Resistance Monitoring programme which co-ordinates activities directed at the emerging problem of antimicrobial resistance in hospital and community bacterial pathogens worldwide, antimicrobial resistance has long been the concern also of several of the specialised WHO programmes. These activities are summarised below.

24. *Antimicrobial Resistance Monitoring (ARM) programme. Division of Emerging and other Communicable Diseases Surveillance and Control (EMC):* The ARM programme started in 1997 setting a goal to reduce the impact of antimicrobial resistance by improving the surveillance of resistance and promoting the correct use of antimicrobial agents worldwide. The ARM programme works with countries to strengthen laboratories through laboratory training, the use of a standardised software developed by WHO to capture and analyse data, and by introducing quality control and proficiency testing. The ARM programme also sponsors national workshops where leaders from various disciplines and institutions develop plans of action for antimicrobial resistance

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monitoring and the use of anti-infective drugs. The goal of the workshops is to establish national networks to characterise antimicrobial resistance in the country and policies for antimicrobial use and infection control. The international strategy of ARM is to build partnerships between the many parties with an interest in antimicrobial resistance (e.g., governments, NGOs, professional societies, academia and the pharmaceutical and diagnostics industries). The objective of ARM is to bring together existing and emerging national and regional networks into a "Network of Networks" to facilitate the global exchange of surveillance data and information. Relevant information on policies, guidelines, bulletins and other information will also be available in a resource bank of reference material to share. Efforts are also being made to establish antimicrobial resistance monitoring in bacteria from food animals and food of animal origin.

25. *Gonococcal Antimicrobial Susceptibility Programme, GASP (EMC)*: GASP is a multicentre programme of continuous surveillance of the antimicrobial susceptibility of *Neisseria gonorrhoeae*. The programme started in the WHO Region of the Western Pacific in 1992. Data are generated by participants in focal points in 16 countries throughout the region and collated in the regional reference laboratory located in Australia. The coverage ranges from a single centre in a geographically small area such as Singapore to country wide networks as in Australia and China. The centres examine susceptibility of gonococci to a recommended "core" list of antibiotics using one of the recommended standard methods. A programme-specific quality assurance programme is conducted annually and a series of reference strains pertinent to the regional patterns of resistance are made available. A similar surveillance network, co-ordinated by a GASP reference laboratory in Ottawa, operates in the WHO American Region, and a scheme is now being initiated also in the WHO South-East Asia Region.

26. *Global Tuberculosis Programme GTB*: Recognising the challenge posed by multi-drug resistant tuberculosis to TB control, GTB established with the International Union against Tuberculosis and Lung Disease (IUATLD) a system in 1994 to survey the extent and severity of anti-tuberculous drug resistance worldwide. The overall aim of the project is to improve our knowledge of the severity and extent of drug resistance worldwide and the performance of national TB programmes through policy recommendations on treatment. The strategy is to collect data on the prevalence of resistance to anti-tuberculous drugs in a standardised manner at country level worldwide, particularly in countries identified as priorities for assistance; and to help countries develop a system of surveillance of resistance and improve the diagnostic capacity of laboratories. The system is built on a network of 22 supra-national reference (SRL) laboratories in all continents to ensure proper laboratory testing procedures. Special surveys or surveillance have been established in over 40 countries and are pivotal in focusing action on problem areas where control programmes must be improved. To ensure comparable results on the extent of resistance to antituberculous drugs, a set of guidelines were developed and distributed to national governments and research institutions. The three main principles outlined in the guidelines are:

- (1) to establish representativeness of the sample of patients studied and carefully calculate its size;
- (2) to implement standard methods of data collection which regularly differentiate between new and retreatment cases of tuberculosis in order to differentiate between primary and acquired drug resistance; and
- (3) to utilise an internationally accepted laboratory methodology for testing resistance and to introduce an external quality control system.

Inter-laboratory quality control of drug susceptibility testing is done within the network of SRLs on a regular basis. In turn, national laboratories in charge of the laboratory component of the survey/surveillance exchange strains with the SRLs, thus making results from all over the world comparable. The results of the first four years of activities will be presented in 1997 in a GTB publication.

27. *Malaria Control, MAL, Division of Control of Tropical Diseases*: The programme maintains a database on antimalarial drug resistance world wide. Information from the data base is available directly to countries. It is also presented in the annual report on the malaria situation in the world published in the *Weekly Epidemiological Record* and in the recommendations on the protection of travellers in *International Travel and Health—vaccination requirements and health advice* which is revised annually. Recommendations for treatment of uncomplicated malaria and methodologies for monitoring and assessment, including monitoring of therapeutic efficacy were presented in the report (WHO/MAL/94.1070) issued after a consensus meeting in 1994. The recommendations for monitoring of therapeutic efficacy were evaluated in four African countries in 1995 and are now being introduced in countries through workshops. The recommendations take into account that *in vitro* tests, although not suitable to set drug policies, are useful for determining cross-resistance patterns and temporal and geographic patterns in parasite resistance. Training material has been developed on the rational use of antimalarial drugs with guidelines for non-pharmacists selling antimalarial drugs as well as for pharmacists. Health education material aimed at community health workers and the general public has been developed. The world's worst antimalarial drug resistance problem is at the Myanmar—Thailand—Cambodia border areas where the programme is developing an antimalarial drug resistance monitoring programme together with the WHO Offices for South-East Asia and the Western Pacific.

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28. *Division of Child Health and Development, CHD*: CHD promotes the rational use of antimicrobial agents in its manuals and in its drug management courses. The programme also educates the public regarding unnecessary antimicrobial drugs, and promotes standards of hygiene including safe water and food hygiene, in the community. A manual for surveillance of *Streptococcus pneumoniae* and *Haemophilus influenzae* developed with the US Centers for Disease Control and Prevention aims at assisting countries in developing and gaining acceptance for guidelines for appropriate selection and use of antimicrobial agents. A manual for antimicrobial resistance surveillance is being field tested in four countries. A preliminary plan has been formulated for appropriate response to outbreaks of resistant organisms. Areas for research include new antibiotics for acute respiratory infection and evaluation of simple and inexpensive tests to identify resistance which is otherwise difficult to detect.

29. *Product Research and Development, TDP, Special Programme for Research and Training in Tropical Diseases, TDR*. A primary objective of the programme is to combat the emergence and spread of resistant organisms. Malaria is one of the six diseases included in TDR, and serves as an example. TDP focuses on the discovery and development of new antimalarials with novel mode of action. The programme furthers research to improve the understanding of mechanisms for resistance, to improve the use of available antimalarials and drug combinations to slow the pace of resistance, and to quantify the benefit of improved patient adherence to drug regimens. TDP encourages the discovery and development of compounds that may modulate or reverse resistance; assesses the use of adjunct treatment, particularly in severe malaria; tests alternative interventions for ensuring patient adherence to full oral regimes. The programme is concerned that drugs meet international requirements in terms of pharmaceutical, non-clinical and clinical development.

30. *Division of Drug Management and Policies, DMP*. The Division promotes the rational use of antimicrobial agents in a variety of ways. On the basis of information from surveillance of resistance, it revises every two years the *WHO Model List of Essential Drugs* which includes a selected number of well-established antimicrobial agents. It also issues prescribing guidelines on infectious diseases. DMP assists governments in improving their systems of quality assurance through activities such as training courses, assisting in implementation of *WHO Guiding Principles for Small National Drug Regulatory Authorities* and the setting up of national or regional quality control laboratories. It is also responsible for the *WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*. A programme on counterfeit drugs has been the focus of much activity for the past three years and many guidelines have been issued on this problem. Control of promotion of antimicrobial agents is addressed in *WHO's Ethical Criteria*. Continuing education of the prescribers and pharmacists is also addressed by DMP.

31. *Action Programme on Essential Drugs, DAP*: The WHO Action Programme on Essential Drugs actively supports WHO's Member States, and especially those in developing and newly-industrialized countries, to rationalize drug treatment, including the use of antibiotics. The core elements of its approach are to promote the development and use of treatment protocols and essential drugs lists, for the supply of drugs, for basic and in-service training of health workers, and for public education. Currently the Programme supports programmes in at least 80 developing countries and over 120 countries have developed national lists of essential drugs.

32. *Action Programme for the Elimination of Leprosy, LEP*: The increasing resistance to dapsone and the indication of resistance to rifampicin in the 1970s demanded a new treatment approach. Fortunately, at the same time some new drugs were released and found to be effective against *Mycobacterium leprae*. The new standard regimens recommended by WHO in 1981 was based on the use of several drugs together. Multidrug therapy (MDT) for multibacillary leprosy now relies on a combination of rifampicin, clofazimine and dapsone for a period of 12 months. The regimen for paucibacillary (PB) leprosy is based on rifampicin and dapsone given for a period of six months. Since the introduction of MDT, LEP has collected scientific evidence on safety and efficacy and published the results to inform both scientists and national programme managers. The programme has actively promoted the use of MDT in national leprosy control programmes by negotiating with the pharmaceutical industry to lower the costs at maintained quality, by promoting the use of calendar blister packs, and giving direct support to some programmes to obtain MDT. In 1995, a global drug fund was established to purchase and distribute high quality MDT drugs, free of charge to all endemic countries and reaching all patients is now a LEP priority. Since the introduction of MDT in 1981, more than eight million patients have been cured. Relapse cases are investigated to explore the possibility of resistance but to date there is no evidence of *M. leprae* resistant to MDT. As part of the surveillance activities, WHO collaborating centres test drug resistance from biopsy materials from relapsed cases.

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Examination of witness

DR ROSAMUND WILLIAMS, Laboratory Training and Support, Division of Emerging and other Communicable Diseases Surveillance and Control, World Health Organization, was examined.

Chairman

110. Dr Williams, good morning, and thank you very much for coming along.

(Dr Williams) Thank you.

111. Would you like to start off with any general comments.

A. The WHO has been looking at antimicrobial resistance for some time, particularly in the Collaborating Centre in Boston under Dr Tom O'Brien and I believe some of you may be visiting that Collaborating Centre in the near future. In 1995 the World Health Assembly passed a resolution which set up a new division which is the Division of Emerging and Other Communicable Diseases Surveillance and Control which is conveniently known as EMC. In that division in Geneva, the **Antimicrobial Resistance Monitoring programme** was included, so what we have had is effectively a shift into the headquarters of the main part of this programme. The programme in Geneva is largely funded by extra-budgetary funds and that means that as it is the end of a biennium, there is a slight nervousness about funding in the new biennium. We have a large amount of funding from the Department for International Development from the United Kingdom for which we are very grateful, both for the division, and for this particular programme.

I would like just to summarise for you the goals of the Antimicrobial Resistance Monitoring programme because I think that helps to set it in context. First of all, although we are called resistance monitoring, our goals are not confined to the surveillance of resistance, but more to assisting countries to establish resistance networks, and encouraging the rational use of antimicrobial agents. In this latter goal we work with our other partners in other divisions in WHO, particularly in specific disease programmes where they are facing one disease and one set of treatments, and together attempt to reduce the rate of emergence and spread of resistance. In one sense, unusually for WHO programmes, antimicrobial resistance is not something we can expect to eradicate or eliminate. It is also unusual in that it is one of the programmes that really does touch every Member State and it is not just a problem in the developing world, but also in the developed world: a severe problem in all of our Member State countries. In the evidence I have presented to you, which was put together by myself as the co-ordinator of the resistance monitoring programme with input from the members of the task force (which is a cross-divisional committee that works across the divisions in WHO with the people who have an interest in resistance), we have highlighted five areas that we felt needed to be covered and I want just to address these headings, particularly the first four: those are surveillance, education, regulation and research. I think the public health infrastructure is an aspect that we could perhaps come

back to in the questioning if you have further comments.

With regard to **surveillance**, the goal of our programme is to assist countries to develop networks. It is not WHO's goal to set up a stand-alone network for resistance monitoring, but more to assist countries to establish national networks and for doing this, we have available a software which is known as WHONET. This is a software which has been developed originally in the Collaborating Centre in Boston and is under further development in WHO in Geneva. It is freely available to anybody who wishes to use it and indeed we have had discussions already with United Kingdom colleagues about the possibility of using it in a United Kingdom surveillance network. It is not a stand-alone laboratory management system and many laboratories already have computer systems in place and we have also a software that allows them to download from their existing laboratory management software into WHONET which then gives them the opportunity of sharing data from one laboratory to another and also to share the data with WHO if they wish. This is certainly the case for a number of countries, particularly countries in the developing world where we can give them user support in analysing their data and show them how they can use it best at the local and national levels. You ask about the developing countries and how they can cope with the standards of WHONET. What we are really saying is, "Can they cope with the standards of antimicrobial susceptibility testing?" We are, as you have already heard, using as a surveillance tool, laboratory-based tests which are carried out as part of a normal diagnostic work-up in a microbiology laboratory. In our experience we find that in each country at least some laboratories have this capability and the main needs they have are for improving their technical skills, particularly in the areas of quality assurance and quality control, of having reliable access to reagents of a suitable quality to carry out the tests and to have a sustainable access to these reagents, and in understanding what to do with the data when they have got it and I think that is true not only in developing world countries, but probably also in the developed world. We have a number of constraints in surveillance and one constraint is that it is based at the present time on laboratory-based collection of data. There is no single accepted global standard method for collecting these data. There are efforts at harmonisation of the laboratory tests both across the European countries and the European Union. A number of countries use the already well-established National Committee for Clinical Laboratory Standards methods in the US, but a number of countries have their own methods and within a country different methods may be used by different laboratories. This clearly poses a big challenge for collecting data across different organisations in different countries where you are very much looking at apples and pears and saying,

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"What does this mean?" and this is certainly one of the major challenges which is faced. Another difficulty which I think you have already highlighted is that of denominator—what are we going to count as our denominator? As a way of illustrating the challenges posed, and this really echoes very well the comments of my colleagues earlier on, we have at the moment absolutely no measure of the number of people who are exposed to resistant organisms and by this we can take "exposed" in the very widest sense, whether that exposure be environmental exposure to antibiotics, through resistant organisms in the food chain, through cross-infection, etc. We do not know how many people are infected with resistant organisms but show no symptoms of disease. We could find some way of measuring those people who manifest disease and seek medical attention and here the idea of using sentinel surveillance, particularly for community surveillance, is a very positive one. We are dependent in a laboratory-based system on the collection of clinical specimens, on the correct isolation and identification of the bacteria that are causing the infection and on the generation of a report. At present we are using as our denominator the number of isolates collected and the number of isolates that were resistant, and clearly that hides a large amount of the iceberg. You have also already heard about the fear that these data tend to be biased because the most serious infections are those that are sampled and those that have failed treatment, so we may be biased in the sense that we collect more resistance than we should do for the number of people exposed. The software that we have and the systems that we are assisting countries to set up do not exclude community surveillance, but they do tend to bias it to hospitals and to serious community infections because of the requirement to take specimens and to examine isolates.

You comment on the evidence from the Association of Medical Microbiologists about the United Kingdom or Europe putting its house in order first and you ask the WHO what its view is on this question. The WHO has a mandate to represent all of its 191 Member States and I cannot agree that we have to put Europe in order first; I think we have to work with every country that requires and requests our help. What is more, I think we have to be aware of how easily resistance travels between countries and where a resistant organism that may not be serious in the United Kingdom may be imported into the United Kingdom by people travelling to other countries. A further difficulty with the surveillance which we have already alluded to is that the data are incomplete and scattered. What we are doing as part of the programme is to try and build what we call a "network of networks" on an electronic database in order to gather the information about surveillance that exists and to allow countries that are establishing their own networks to feed their data into this network and to compare it with other countries. Also to look at the sort of surveys that are going on in other countries, but without pooling the data into a single database, so we are not mixing the apples and the pears, but we are saying, "In this country there are some apples and they look like this, and in this country there are some pears and you can look at those". This

is now available as a prototype in an electronic format on the World Wide Web.

I return to the question of **travel**. Data that we have from the World Tourism Organization in 1995 showed that 36 million people left the United Kingdom to travel in Europe and 18 million people from Europe visited the United Kingdom. 6 million people from the United Kingdom went to developed world countries and a further 1 million to developing world countries and all of those people you may expect to encounter different resistant organisms and there is the possibility of bringing those resistant organisms back to the United Kingdom. The travel element means that we cannot consider one country in isolation, but that the spread of resistance by people moving resistant organisms around is a very significant one.

112. You said that the Department for International Development, what was the ODA, handsomely supported you, but in terms of general **resources**, are you constrained by budgets?

A. Yes, we are significantly constrained by budgets. As I say, the programme is supported almost entirely by extra-budgetary funding. That means that it is not part of the regular WHO budget, the funding for this programme, and so we are in a situation in a sense rather like looking for grant money.

113. Could I ask whether the United Kingdom pays her share in relationship to other developed nations as a proportion of GNP?

A. Yes, the United Kingdom is paying her share and there is no doubt that she has supported WHO and the programme extremely positively. We also have a number of trainers who do our laboratory training courses who are based in the United Kingdom. As to whether you could do more, one of the things which would be very helpful from the United Kingdom would be the possibility of **seconding people** to the programme in Geneva. There is an amount of expertise here which would help us move forward our programme and I think it would have a collaborative effect because people could experience the problem in a wider situation and bring that experience back to the United Kingdom.

Lord Perry of Walton

114. You have given us your first objective, which is to develop **surveillance programmes in the different Member States**. Could you give us an indication of what proportion of Member States have got anything that is even reasonable in terms of surveillance?

A. I think it would be fair to say, if we could go by WHO region, roughly speaking, that the region of the Americas, including all the South American countries, are reasonably well aware of the need to develop surveillance, which is the first step. If you go to the European region, we have really a split between Eastern Europe and Western Europe. You will be aware that the WHO region for Europe goes to the Urals more or less and includes all the newly-independent states where there is a major problem of resistance and a total lack of surveillance.

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[Continued

[Lord Perry of Walton *Contd*]

In the Eastern Mediterranean region there are beginnings of surveillance networks in some of the countries. In Africa we have fairly elementary surveillance in a few countries, and we have done some work in Kenya and a number of other groups have been working in some of those countries. We have been particularly focusing on the Western Pacific and South-East Asia because some of our donors have had a particular requirement that it is there that we should spend the money and I would say about half the countries in those two regions have some surveillance going on. That is to say we have surveillance; that is not actually saying what quality those data are, how reliable they are or the use of them.

Lord Walton of Detchant

115. Just to follow up the point which you made about **secondment** of people to go and work on this programme of the WHO, I have been involved in a totally different area in collaboration between non-governmental organisations and the WHO in the field of clinical neuroscience and we had a number of volunteers, senior people, who were very prepared, at WHO's request, to go and work in Geneva in this field. But WHO found itself quite incapable of offering accommodation, even limited secretarial support or any kind of access to offices or telephone facilities. Are you in that position?

A. We undoubtedly have a space problem, but I should think that is probably a characteristic of most big organisations. I think I would not make the offer if I could not provide the space and the telephone and other facilities which were needed to work.

116. You could provide it?

A. Yes.

Lord Rea

117. You did say that the **finance** is precarious on a year-to-year basis. With surveillance of an ongoing problem, it seems strange that it is not part of the regular budget. Could the British Government do anything more towards putting it on a more secure financial footing?

A. Well, thank you, that is a very nice question to hear! We have in fact made a proposal to the Executive Board for a resolution to be placed in the next World Health Assembly in May specifically concerning antimicrobial resistance. We hope that this will both bring it to the notice of the Member States and also assist in putting the financial aspects on a firmer footing.

Baroness Masham of Ilton

118. What happens to the countries who do not use **WHONET**? Do you try and encourage the governments?

A. We try to encourage the governments if they are lacking a system. To countries which already have a system in place and do not find any fault with it, so to speak, we say, "Fine. We have a software which

will allow you to download your data to us if you want to share it with us". I would have to say also, going back to a previous question, that whilst surveillance exists in many countries, surveillance networks, ie national networks, are very few and far between.

Baroness Platt of Writtle

119. May I ask about the WHO's efforts to **educate practitioners and patients** and also how receptive the audience is.

A. Yes, I brought for you some examples, particularly of educating patients. As you are probably aware, there is a recent document from the BMA Patient Partnership about coughs and sneezes. There are also similar sorts of documents that are going to patients in the community in the US and there are copies of these here for you if you are interested and both of those specifically recognise resistance as a problem. I think there is a lot of activity particularly in the developed world countries, including obviously Europe and the US, about trying to educate patients against overuse of antibiotics. What I am not aware of are any programmes yet to evaluate the effects that those educational programmes have and this is certainly one of the things that I would comment on under the research heading. I think we need to look at the impact of education programmes and ask, can we change practice by this sort of programme?

120. And then there is the demand in the developing world too because they are demanding antimicrobial agents without prescription and then not using them properly.

A. Absolutely.

121. And that must be one of the biggest problems that you face.

A. Yes, one of them.

Baroness Masham of Ilton

122. On your education list, you have not got nurses. Are they not the biggest number?

A. I think that is a very good point, thank you, yes. Clearly nurses play an invaluable role and we are working very hard also to stress the importance of infection control in that stopping the spread of infection will stop the spread of resistance or help to stop the spread of resistance, so yes, thank you for that point.

Lord Winston

123. What actually is your **budget**?

A. The budget plan I have for next year is a budget of \$1.6 million for the biennium 1998-99.

Chairman

124. Perhaps you would like to carry on with education.

A. I think just to continue on the element of education, if we were to put it under two big headings, we try to educate the generators of the data, in other

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words, the people who do the tests and produce the data, how they are going to use them and communicate them, and people who use the data, be they physicians, nurses, pharmacists, but also people who make the policy at a higher level in ministries of health, for example. This is the aim of our **national policy workshops** and I would like to make clear, that the national policy workshops are not directed just at how you write an antibiotic policy; they are to bring together really a cross-section of policy-makers, physicians, pharmacists, nurses and plus the pharmaceutical industry in a country, to look at surveillance if it exists, or, if not, how they will establish surveillance in a country, how they handle the question of rational prescription at a national level, in other words, do they need more education or do they need to change regulations, and the influence that regulations on prescribing can have in countries. The output of that workshop is a national plan of action. We have carried out such a workshop now in three countries in the last year, in Indonesia, in Kenya and in China, and we have three more planned in the next four months, in Sri Lanka, in India and in Myanmar,¹ and these are countries where we are obviously often starting from scratch and people are saying, "Well, we think we have a big problem and we do not know what we are going to do about it", so the national policy workshops include how you write an antibiotic policy, but it is not the only thing that is there.

125. Translating this into action in different sorts of communities on a global basis must be quite a formidable challenge.

A. Yes. I brought some documents as an illustration which I am happy to leave here concerning guidelines for treatment and how they are presented. Basically, as you know, the WHO has a number of vertically organised programmes around particular diseases and those programmes are responsible for drawing up guidelines for treatment and that includes antimicrobials and, where appropriate, antimicrobial resistance. There is also, as I am sure you are aware, the model list of essential drugs which is used by many countries to decide on their basic drug list and that is now being revised with input from our programme on resistance and the need to change or to monitor the model of the essential drugs on the basis of the local resistance problem.

Baroness Platt of Writtle

126. You mentioned that the WHONET is freely available. Could you tell us what sort of take-up there is throughout the world?

A. Yes, I think to give you a correct answer, I should do that in writing, but it is well taken up.

Chairman

127. Please carry on.

A. I think I have been particularly struck as I have been working on this programme at how education

may be able to do so much, but in a number of countries, or in all countries, regulations are essential and in a number of them they are severely lacking. There are important needs to regulate the promotion and the sale of antimicrobial agents and their advertisement and the need for the **pharmaceutical industry** to comply with the law and with the guidelines for the ethical promotion of antimicrobials and to behave responsibly in this area. We have been trying to build bridges with the industry in this programme. WHO has not had a particularly happy history in its dealings with the pharmaceutical industry on all occasions and we have been very much trying to seek ways in which we can find parts of the common agenda here. I think the industry is somewhat schizophrenic in its approach to resistance because, on the one hand, a little bit of resistance to somebody else's drug will sell your drug and, therefore, there is an advantage to a small amount of resistance. It undoubtedly recreates a market so that when the drug is going off patent, there is a chance that if you have got a new one, you will be able to sell it because it is active against resistant strains, so in that sense the industry is not wholly against a bit of resistance, but, on the other hand, the industry wants very much to be seen as being socially responsible and I would say that they are doing a lot more now in considering resistance.

Lord Porter of Luddenham

128. In your memorandum at paragraph 20 on that point you say that the pharmaceutical industry must be encouraged to develop new antimicrobials, but how do you encourage the pharmaceutical industry? What form does the encouragement take?

A. I think the encouragement takes three forms. The first is to remind and to provide data for the industry on the potential market size for new drugs. The industry is very focused on approximately eight countries for its market. The market is clearly much bigger than that in terms of infectious diseases and the challenge is whether that is a market that can actually support the purchase of drugs and one of the areas where you may be aware that WHO has been working particularly on tropical diseases is in trying to develop, in collaboration with the industry, agents which otherwise would not go through the clinical development pathway, so that is, I think, one area where we can stress the need and we can show the need that resistance brings.

Lord Jenkin of Roding

129. I wonder if I could turn to what you were saying a moment ago about the pharmaceutical industry and the degree of responsibility with which it approaches this; in your paragraph 16 you say that this is all regulated by national authorities—licensing, imports, commerce and so on, and you have developed guidelines. I understand that last November you had a meeting between the International Federation of Pharmaceutical Manufacturers' Associations and yourself where you agreed a framework for future

¹ Burma.

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[Continued

[Lord Jenkin of Roding *Contd*]

collaborative efforts to contain the spread of antibiotic-resistant bacteria. I wonder if you could tell us a little bit more about this and whether you feel this is going to be effective.

A. Certainly. I will leave with you the document which is a report of that meeting which has the details for you. I think what we agreed at that meeting was that there were opportunities where we could work with the industry or they could work with us. The first of these was in sharing information. The industry, and I say "the industry" collectively, but a number of the major pharmaceutical companies have now established surveillance themselves in large networks under various different names, using clinical isolates collected from hospitals, and what we are hoping is that the industry will share with us those data at a level at which we can make them available so that anybody can access the summary data. So far our discussions following that meeting have been cautiously positive, let us say.

130. Do you find the ABPI, our own association, helpful in this regard?

A. They have not come back to us specifically on that, but we have a number of bilateral meetings with individual companies on this particular issue.

Lord Walton of Detchant

131. We have been told that there is some recent evidence from **Denmark** of the impact of firm government action on the rates of resistance.

A. Yes.

132. Can you explain that to us?

A. The Danish have, I think, managed in some counties of Denmark, so this is not universal across the country, to collect data on prescriptions, daily defined doses per thousand population in both the community and in hospital, they have collected data on resistance in certain pathogens and they have done some surveys of healthy people and people in particular occupations where they might be exposed to non-human uses of antibiotics, such as in the agricultural industry. They have very strict national prescribing guidelines and, by having the data about prescribing and having their guidelines, they can actually identify which doctors are not prescribing according to the guidelines. Lastly, they have a very firm isolation policy for potentially infectious people, so that, for example, going back to the travel issue, if you have travelled and fall ill and are admitted to hospital in Denmark, you will be isolated until you have been screened and shown to be free of resistant pathogens.

Lord Rea

133. What sanctions are applied in Denmark to doctors who persistently prescribe against the guidelines?

A. I understand that they get a series of increasingly severe letters, but whether they can

actually be struck off, I do not know. The document¹ may give you that information.

Chairman

134. Would you like to carry on with regulation?

A. I just wish to draw to your attention that whilst it is not the situation in the United Kingdom, in many countries in the world **the person who prescribes the antibiotics is also the person who sells them**, in other words, who makes their income from the prescriptions. I have just recently come back from China. They were telling me that 60 per cent of both the doctor's and the hospital's income comes from prescriptions and until that sort of thing is separated, no amount of education will change a doctor's prescribing habits if his income is dependent on it.

Lord Jenkin of Roding

135. As I understand it, that is the main reason why the consumption of drugs of all sorts in Japan is far above that of most other developed countries.

A. That is certainly also true, so it is not only a developing world concept, but also that of a number of other countries, but I think it is critical to this issue. Perhaps we can come to the control of non-human uses, addressing your questions about **animal husbandry** and also related to that, the electronic discussion group. WHO at the present time does not have a stated policy on non-human uses or use in animal husbandry. The meeting that WHO sponsored² from which I have the press release if you are interested in it here, has drafted some consensus statements where it wishes to proceed towards policy in partnership with the FAO. I think the key recommendation from that meeting, and I would say to you that this is in draft as it was only discussed last Friday, is that concerning the use of antimicrobials in growth promotion in animals. Antimicrobials should not be used that are known to have human therapeutic uses or are known to select for cross-resistance to antimicrobials used in humans. This use in growth promotion should be terminated. There is no timescale on that, you will notice, and I would say again that this was the subject of a large amount of discussion. There were a number of countries representing the European Union, but also a number of developing countries, and you will be aware that the amount of meat produced in the developing world is now about 40 per cent of the world's consumption and is rising, so again it is a question where we cannot ignore the resistance in the developing world.

Chairman

136. One of the interesting developments in the food chain recently in this country of course and elsewhere is the quality assurance schemes where large

¹ "Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark" No 1, Feb 1997, ISSN 1397-078X.

² WHO Meeting on the Medical Impact of Use of Antimicrobial Drugs in Food Animals, Berlin, 13-17 October 1997.

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DR ROSAMUND WILLIAMS

[Continued]

[Chairman Contd]

supermarkets will demand certain production methods of their providers. Do you see that this is maybe one route through which there might be some control of growth promoters and of antibiotics?

A. I think that certainly the market will drive it in many countries, yes. There have been some studies in Scandinavia showing that if they market meat that is labelled saying, "These animals were reared without any growth promoters", that sells well and any price premium is not a problem. I do not think that will be true in many parts of the world though.

137. And there are a number of organisations, some of which we will hear from later on in our investigation on this, but presumably you are in contact with them on an informal basis even though there is no definite policy of WHO.

A. Exactly, the meeting that was held last week was to address the issues about use in animal husbandry and there were representatives from FEFANA, COMISA and from FEDESA all present. Part of the group that I co-ordinate in WHO has the responsibility for looking at antimicrobial resistance in bacteria from food animals and food of animal origin and one of the other outcomes of the meeting was a recommendation for surveillance and we need to look at how we would tie that surveillance into surveillance of resistance in humans.

138. Thank you.

A. One of your questions concerned the need for further **research**. I think there are a number of needs underneath the heading of surveillance that should be addressed but particularly I think we have to find ways to improve the correlation between the laboratory data and clinical outcome in terms of actually understanding how good the laboratories' resistance detection is as a marker of the likely failure of therapy. Whilst it is clear for some infections in some circumstances it is much less clear for other infectious conditions such as infections of the respiratory tract. There is a clear need, which I have illustrated and I am sure other colleagues have also, to see how we can better access the denominator data so that we can really carry out a risk assessment of resistance in this country and others. We have already alluded to the question of how effective is education. I think there are a lot of education initiatives going on now and we would be well advised to spend some research money on looking to see whether those initiatives are effective rather than spending all the money in setting up the initiatives. I think we have identified within our programme at WHO a particular need to try and design and test some indicators of successful impact. In other words, we have set up some clear but far-reaching goals and we need to define how we are going to measure whether we are reaching those goals. We will be looking for a fall in the number of resistance isolates or reducing the cost of prescribing, a number of different indicators that could be used, and I think there is a need to study those in some detail. I come back to the development of **new agents** which in a sense is a circular argument because if you develop new agents they will be used and then we will get resistance to them etc, but until recently many of the

major companies decided they would pull out of development of new antibacterial agents because they felt that infectious diseases were a lessening problem in their market countries and because the problems of, for example, neurological diseases and the markets associated with them were more attractive. I think it is fair to say that many of those companies have reversed their trends and are now more interested in developing antimicrobials as we were talking earlier and that should be encouraged. I think also that we need to look in a global sense to see how we can do more to prevent some of these infections rather than require to have antibiotics to treat them. Just looking at the impact that the *Haemophilus influenzae* vaccine has had in preventing infection with *Haemophilus influenzae*, the resistance problem with *Haemophilus* could be set aside to a large extent if the infections were no longer a problem. So I think there is a need for going beyond simply developing new drugs and developing other treatment strategies.

139. Where is the majority of research in this area done? Is it in public health laboratories, universities or pharmaceutical companies?

A. I would say that the majority of research in terms of looking for new antimicrobial agents is done in or stimulated by the pharmaceutical industry often now in collaboration with small biotechnical companies or universities with academic research at the early research stage. Of course the whole of the period from clinical development to the marketing is done in the industry.

140. As Professor Percival said in previous evidence, often a lot of this research is not "sexy" enough to get money from the Research Council which is unfortunate. Having been associated with the tropical diseases programme in WHO I know they themselves instigated research and funded it but I presume that your budget, whatever it is, is not sufficient to do that. Is there any possibility of special funding for research conducted through WHO?

A. I think the model that you have spoken of is a model that we would like to investigate further. At the moment I do not see any immediate sources of funding that would make that possible and so what I would like to do is to explore the various avenues possible to raise funding on that aspect, yes.

Baroness Masham of Ilton

141. Chairman, could I ask about the Directly-Observed Treatment Short Courses for **tuberculosis** and ask whether they are working.

A. As you probably know, the global tuberculosis programme is covered by a different division in WHO. They have provided for you documents on directly observed treatment. What I think needs to be clear is the DOTS strategy is not simply standing watching somebody take the medicine but also the identification of smear positive cases, the provision of the appropriate drug supply and quality, the supervision of the treatment and the follow-up and the recording and reporting. They did give me figures to show that both in New York and Peru—slightly different places—

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[Continued]

[Baroness Masham of Ilton *Contd*]

where the DOTS strategy has been in place long enough to show an impact, it has actually shown that they have had a significant decrease in the notification of new cases. It takes about four years after DOTS is initiated to start seeing a decrease. Indeed, initially you tend to see an increase because you have a better recording of cases.

Lord Rea

142. Is that approach suitable for any other diseases other than TB?

A. I think it would be suitable for some. Leprosy is the obvious example in the mycobacterial area where you are using a multiple therapy and a long course of therapy. Many of the sexually transmitted diseases seen in the clinic are treated by supervision when the patient is treated in the clinic when he presents to the doctor. It has also been suggested that malaria might be appropriately managed in this way, but it is an enormous challenge.

Chairman

143. We discussed earlier the entirely **new molecules** that might be available. Have you any comments on the classes of molecule that people in the pharmaceutical industry are now investigating?

A. I think from my experience of having worked in research in the industry until recently, there is an interest in two things. One is there is a clear need to have a novel class. We need a class of molecule that has not already been exploited as an antimicrobial. The second aspect presented to you earlier was the idea of using molecules that have not been considered as antimicrobials in the purest sense of the word, if you like. I would say that the interest is there for both. The challenges are slightly different. The totally novel ideas because they are totally novel will require a lot more working up to become viable drugs and therefore, of course, it is a cost issue. I can say from my experience that finding a totally new class of antimicrobial agent is an extremely challenging problem which is therefore extremely costly and the opportunity to modify an existing molecule is one that has certainly up until now been the one that has been preferentially exploited.

144. Of course, the other alternative approach by some to this is **vaccination**. Have you any comments on that as an effective alternative approach?

A. As I say, I think that vaccination in certain circumstances is something that we ought to be continuing to explore. There are a number of projects based not only on the *Haemophilus influenzae* vaccine but also on developing new vaccines against *Streptococcus pneumoniae* and there we have a situation where we have a community-acquired infection and an increasing resistance problem to essentially the only drug (penicillin) that is affordable

in most parts of the world. Then immunisation is an important way forward.

Lord Rea

145. Some of us will be going to the **United States** in about a month and I wonder if you could give us some suggestions as to the things that we should be looking into there.

A. Yes, certainly. Just briefly to say with this specific programme we have two Collaborating Centres in the United States, one in Boston where the surveillance and development of the software originated and the second one in one of the divisions of the Centres for Disease Control where they are responsible for organising the external quality assurance scheme that we use and we provide to laboratories that are working with us. Here I am talking particularly about laboratories in the developing world where the quality assurance schemes are needed and do not exist at present.

Chairman

146. Although we are not going to the pan-American World Health Organization building, do they play an important role in the Americas, Central and South America?

A. Yes, indeed. I think it is fair to say that in each WHO region the regional office plays a significant role. The interaction and the interface between those significant roles and the Headquarters role is one we are working on very hard. We will be holding in Europe this year a meeting on the state of surveillance in European countries and we will be having a similar meeting in the WHO office for the Americas in the first quarter of next year and in the Western Pacific towards the end of next year so that we will be able to bring together the people who are active in each country on surveillance to say what is the status of surveillance in those countries.

Baroness Masham of Ilton

147. Can I just ask one question about the Americas and the problem of education and **language** because with HIV and AIDS and the poor Hispanic people there was a problem with education earlier on and then with the resistant tuberculosis which circulated. How does language work with WHO?

A. There are six official languages but that does not help to answer your question effectively. What we have done so far is to work in English or French with a translator for the local language where necessary. That has been effective for training opportunities but is not so effective for education by leaflets and education in other ways and one of the things we are looking at is essentially how we could fund the getting of the information in the correct appropriate language. Based on the fact that I have only three people working on this project, much of what we do is a partnership and we have a partnership with the National Committee for Clinical Laboratory Standards in the US where we are hoping that they will help us to

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[Continued]

[Baroness Masham of Ilton *Contd*]

provide the documents if we can provide the translation. We have now a tentative agreement to do that in Chinese which will attract at least a billion or so readers and they have already translated documents into a number of other languages. We were also trying to work up a consortium with a group of partners from the industry. The industry is extremely effective at marketing but also at educating the public and we are hoping that by getting together a group they may help us to put together some simple educational material so that we can also afford the appropriate translation.

Baroness Platt of Writtle

148. Following on that, the two United Nations Conferences for Women particularly highlighted the **importance of the mother** and her influence on the

family. I attended at Nairobi, and I did also visit the United Nations Women's Organisation. I wonder whether you work with them in the developing countries in their own language so that they might cooperate with you to issue guidance so that the mother understands the problem and makes sure that the child takes all the prescribed antibiotics.

A. Thank you. We have not been in direct contact with them but that is a very helpful suggestion.

Chairman

149. I think we must draw this to a close. Thank you very much indeed for coming along.

A. Thank you very much for inviting me.

Supplementary Memorandum by the Division of Emerging and other Communicable Diseases Surveillance and Control, World Health Organization, Geneva, Switzerland

WHO COLLABORATING CENTRES

The WHO Division of Emerging and other Communicable Diseases Surveillance and Control (EMC) has a worldwide network of c.200 laboratories and institutions, designated as Collaborating Centres. They are selected on the basis of expertise in bacterial, viral and zoonotic disease diagnosis and epidemiology and carry out specific activities on behalf of WHO. Collaborating Centre activities include laboratory diagnosis, production and supply of diagnostic reagents, and provision of epidemiological and laboratory training, advice and support to developing countries.

The WHO Antimicrobial Resistance Monitoring (ARM) programme in EMC works with two specific Collaborating Centres in the USA:

The WHO Collaborating Centre for Surveillance of Antimicrobial Resistance.

Microbiology Laboratory, Brigham and Women's Hospital, Boston.

Principal investigator: Dr T O'Brien.

The WHO Collaborating Centre for International Monitoring of Bacterial Resistance to Antimicrobial Agents.

Nosocomial Pathogens Laboratory Branch.

Hospital Infections Program.

Centres for Disease Control and Prevention, Atlanta, Georgia.

Principal investigator: Dr F Tenover.

The WHO CC in Boston was first designated in 1985. Dr O'Brien has significant expertise and a long-standing interest in the analysis of data from antimicrobial susceptibility tests and the use of these analyses to show resistance trends, highlight epidemiology of particular resistance phenotypes and to promote infection control interventions. In the early years the analyses were entirely manual but with the assistance of a series of research associates, the WHONET computer software was first developed in Boston. Dr John Stelling was one of Dr O'Brien's research associates and when EMC Division was formed in WHO HQ in 1995 (in response to the increasing concern about emerging and re-emerging infection including antimicrobial resistance) Dr Stelling joined the Division and continues the software development. Dr O'Brien has travelled widely promoting the importance of local resistance monitoring and the value of the WHONET software as a tool for such monitoring. He also acts as a trainer for the ARM programme laboratory training courses in antimicrobial susceptibility testing and resistance monitoring.

The WHO CC in Atlanta was first designated in 1997 and it has the task to manage the external quality assurance scheme that has been set up specifically for the ARM programme. The bacterial strains for quality control and proficiency testing are selected, prepared and shipped to Geneva for distribution. Results are returned

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by the participant laboratories to the WHO CC where they are analysed, and feedback and advice is sent to participants. The QA scheme is still in an early phase with results from 37 labs in 33 countries. In the longer term it is anticipated that laboratories will be encouraged to join one of the existing national external quality assurance schemes (such as NEQAS of the PHLS) until countries have developed their own national schemes. Until such time it is imperative that laboratories are able to benefit from a scheme that will assist them to improve the quality of their resistance surveillance data. Laboratories which perform satisfactorily are invited to enrol in the WHO network and to send their routine results to the ARM programme in Geneva.

WHONET software—Estimate of current or past users (total = 457)

WHO African Region:

Algeria 1
Kenya 4
South Africa 1
Uganda 1

WHO Eastern Mediterranean Region:

Kuwait 1
Morocco 1
Pakistan 1
Saudi Arabia 3
Sudan 1
Tunisia 1

WHO European Region:

Belgium 20¹
Bulgaria 4
Czech Republic 15
Denmark 2
Estonia 1
Finland 10
France 2
Germany 3
Greece 15
Iceland 1
Ireland 1
Israel 2
Italy 10
Latvia 1
Lithuania 1
Netherlands 37¹
Norway 1
Poland 2
Russian Federation 7
Slovakia 7
Sweden 23¹
Switzerland 10¹
Turkey 2
Ukraine 2
UK²

Pan American Health Organisation:

Argentina 25
Brazil 1
Chile 5

¹ Countries where WHONET has been used during a specific study rather than for ongoing "routine" surveillance.

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Colombia 10
Costa Rica 2
Ecuador 1
El Salvador 1
Guatemala 4
Mexico 4
Peru 1
Uruguay 2
USA 10
Venezuela 14

WHO South East Asia Region:

India 2
Indonesia 3
Myanmar 1
Sri Lanka 2
Thailand 5

WHO Western Pacific Region:

Australia 2
China 30
Fiji 1
Hong Kong 3
Japan 3
Korea (Republic of) 80¹
Malaysia 15
Mongolia 2
New Zealand 2
Philippines 13
Singapore 9
Taiwan 3
Vietnam 5

Estimate of current or past users total = 457

PARTICULAR ASPECTS THE COMMITTEE MAY WISH TO EXPLORE DURING THE VISIT TO THE USA

Laboratory aspects

1. The widespread/universal acceptance of the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) for antimicrobial susceptibility test methods and "breakpoints". There is major interaction with the pharmaceutical industry for the setting of breakpoints. Sharing a common test and interpretation method readily enables comparison of data between institutions.

2. There is a requirement for quality control data as part of laboratory accreditation. (It is not clear what action is taken if a laboratory "fails").

Surveillance

3. There is no common surveillance network for antimicrobial resistance for the whole country.
4. Different states have different requirements for statutory notification of infections (and resistance). CDC is notified of unusual resistances.
5. CDC has several different divisions involved in antimicrobial resistance and its surveillance.

¹ Countries where WHONET has been used during a specific study rather than for ongoing "routine" surveillance.

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6. A surveillance "industry" is developing with several private companies devoted entirely to gathering data from health care institutions (by electronic download), analysing these data and maintaining a proprietary database.

Health Care System

7. There are many differences between the UK and the USA but one which may be of interest to consider is the strength of the family doctor (general practitioner) system in UK. Since the majority of prescribing is done in the community, this system is of great relevance.

TUESDAY 28 OCTOBER 1997

Present:

Dixon-Smith, L.	Platt of Writtle, B.
Gregson, L.	Porter of Luddenham, L.
McFarlane of Llandaff, B.	Rea, L.
Masham of Ilton, B.	Soulsby of Swaffham Prior, L.
Perry of Walton, L.	(Chairman)
Phillips of Ellesmere, L.	Walton of Detchant, L.

Memorandum by Dr R T Mayon-White, Regional Epidemiologist and Consultant in Communicable Disease Control, based in Oxford

1. My evidence is based on my experience of working on infectious disease epidemiology in Oxford since 1971. These past 26 years have seen a tremendous change in attitudes to infectious diseases, from a time when they were thought to have been conquered by antibiotics, vaccines and hygiene to the present when it is impossible to see an end to the problems that are emerging. The threat that bacterial infections will become untreatable is one of these emerging problems. My evidence concentrates on infections outside hospital, both those that arise outside hospital (so called "community-acquired" infection) and those whose origins are in hospital but spread into the community.

2. In my experience, and to the best of my knowledge, the study of antimicrobial resistance outside hospitals in Britain has been highly selective, typically focused on a single species or group of micro-organisms, often in one geographical area. My evidence is necessarily selected and consists of examples with which I am familiar.

3. There are some general points that determine the public health significance of antimicrobial resistance:

- If treatment of an infectious disease significantly reduces its infectivity, resistance to treatment increases the risk of spread: pulmonary tuberculosis is a good example.
- If antimicrobial resistance makes some infections more difficult or expensive to treat, or more likely to be fatal, then the consequent increase in mortality, morbidity and/or health service costs are important.
- If antimicrobial resistance is a distinctive marker for one strain of a bacterium, then it may show patterns of spread that require better control measures.
- Most community acquired infections are self-limiting and antimicrobial drugs play little or no part in determining the outcome.

4. Methicillin Resistant *Staphylococcus aureus* (MRSA) is a prime example of an antimicrobial resistant problem spreading outside hospital. Until 1990, the problems of MRSA were perceived to be concentrated in hospital, both in the UK and abroad. In 1991 and 1992, a large outbreak of MRSA epidemic type 16 in Kettering in Northamptonshire (part of the Oxford Region) changed this perception.¹ The change occurred because a type of *Staphylococcus aureus* had evolved which could sustain its methicillin resistance outside hospital, away from the selective pressure of heavy antibiotic usage. The consequence of this evolution was the MRSA type 16 was repeatedly re-introduced into hospital by patients who had become colonised either by previous admissions or by contact with other patients discharged from hospital. Many of these patients were elderly, requiring prolonged care from acute hospital wards, long-stay wards, community hospitals and nursing homes. These institutions collect together people with several susceptibilities to colonisation and the spread of staphylococci: chronic leg ulcers, urinary catheters, dry skin which sheds scales, and the need for much "hands-on" care. The infection control team at Kettering did well to contain the problem as far as they did, but the persistence of the problem and the spread across South East England were inevitable.

5. At first, the Kettering outbreak of MRSA type 16 was managed as a hospital infection problem, with intense screening of hospital patients for MRSA and an isolation ward specifically for any patients found to be positive. As the community spread was appreciated, Dr. Patrick Morgan, who is the local consultant in communicable disease control, became more involved. He developed a local community infection control nursing service, working with hospital teams, but concentrating on precautions that could be taken in community hospitals and nursing homes. When the costs (£303,000) of the isolation ward and its heavy nursing load became too much for the hospital to bear alone, the Oxford Region Health Authority was asked to help. At this point, I assessed the situation and advised that Kettering be given £200,000 as a single payment to resolve the immediate financial crisis, but that any further additional funding should be directed to epidemiological studies and a scientific trial of the control measures. By this time, the Kettering MRSA was present in hospitals in

¹ Cox R A, Conquest C, Mallaghan C, Marples R R. A major outbreak of methicillin-resistant *Staphylococcus aureus* caused by a new phage type (EMRSA-16). *J Hosp Infect* 1995; 29:87-106.

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neighbouring districts, so the hospital in Kettering decided that a less intense regime of isolation was more practical.

6. One of the risks of isolating infected patients was illustrated on the BBC Panorama programme on MRSA last year, which showed an elderly woman isolated in her own home, and her children and grandchildren afraid to touch her. This image made a big impact on viewers, especially on the staff of nursing homes and residential homes, and the families of people affected by MRSA. Since that programme, consultants in communicable disease control and the community infection control nurses who work with us, have spent many hours re-assuring people that the risks of MRSA outside hospital are very small, that a clinical infection could be treated if it were to occur, and that the strict control measures used in hospital do not apply in the community. A good thing to have come out of this scare is that the role of the community infection control team is well established in the 79 per cent of health districts with community infection control nurses. Unfortunately, health districts which do not have community infection nurses are less able to give infection control teaching to community care personnel, to promote local and national policies, to liaise with hospital infection control teams and to maintain surveillance.

7. Surveillance of infections in the community is one area of weakness in our response to MRSA in particular and antibiotic resistance in general. At the end of 1992, it was clear from the Kettering experience that MRSA was becoming endemic. The hospital infection control doctors in Oxfordshire reported all people newly diagnosed as having MRSA to my community infection control nurse and me. A practical purpose was to enable us to anticipate questions from community carers and to facilitate discharge from hospital. An important by-product was a data-base of every patient, in and outside hospital, known to have MRSA colonisation or infection. Hospital staff who have colonisation detected by screening are not included in the data-base, but patients found to be carriers in an outbreak are included. The data-base has been kept simple, with very limited clinical and microbiological data. Nevertheless, it has enabled us to follow the rise in the number of Oxfordshire people with MRSA for a period of nearly five years (figure 1). Several features are apparent from this surveillance of 1,074 patients. Firstly the rise was exponential from 1993 to early 1996, since when local control has become more successful. Secondly, there is a seasonal pattern, which we attribute to the heavy hospital case-loads in winter, which was a crisis point in January 1996. Thirdly, there is an increasing number of patients who were transferred to Oxfordshire hospitals with MRSA from hospitals and homes outside the county; and this rise has continued after acquisition in local hospitals was stabilised. These 'imported' patients (including five patients from abroad not shown in figure 1) make up 23 per cent of patients whose MRSA infection/colonisation was first detected in Oxfordshire. The fourth feature is the modest, but important, increase in MRSA acquired in nursing homes (44 patients, 5 per cent of those with MRSA acquired in Oxfordshire) or at home (71 patients, 8.5 per cent of local patients). Almost all of these 115 community-acquired MRSA cases were diagnosed from swabs submitted by general practitioners and community nurses or clinical reasons, i.e. for suspected infection.

8. Such local surveillance, as I have described, is of limited value on its own. To be more useful, a comparison with other areas is needed. The patterns of increase and the scale of the problem appear to be similar in the other three health districts in the former Oxford region (Berkshire, Buckinghamshire and Northamptonshire), but hitherto we have not standardised our surveillance methods. The Public Health Laboratories in the Anglia and Oxford Region have started a project to pool our data on MRSA in a common format, and this should lead to standard methods and to valid comparisons of incidence and control policies. These developments have to fit into such time as is permitted by urgent and routine work, and within existing resources. There have been several valuable ideas in the region, particularly for the survey of the prevalence of MRSA in nursing and residential homes, which have been deferred because research and development funding was unavailable.

9. Another weakness, illustrated by MRSA and related to the under-developed surveillance, is a lack of a strategy for the control of MRSA. There are policies and guidance on what should be done at the district level, but there is little national co-ordination or direction. Yet it is obvious from the experience in this region and elsewhere that the spread of antibiotic-resistant infection is national and international. If there was a strategy, which might be to contain the incidence of MRSA to its current levels in British hospitals, and to its current prevalence in the community, then it should be possible to decide on the appropriate control policies, and agree on a monitoring programme. Without such a strategy, it is unlikely that control measures will be consistent enough to prevent further increases. Unless every hospital is working to the same standard and to a shared objective, it is too easy for hospitals to give up rigorous control when it seems to be expensive or restricting hospital activity.

10. One of the key messages which is in danger of being overlooked is that MRSA is a marker of cross-infection in hospitals and community care. This is a reason why many of the infection control teams in hospital and in the community give time to the control of MRSA. This is more important now that MRSA is endemic, and focuses on the basic hygiene practices: hand-washing, good cleaning, availability of the right equipment, adequate ventilation, the avoidance of overcrowding, alertness to the early signs of infection and promotion of co-operation.

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11. Tuberculosis is a second example of an infection whose resistance to antimicrobials has earned the title of "super-bug". My local experience of multi-resistant tuberculosis is in line with most of Britain outside London. The clinicians in Oxford hospitals who see patients with chest diseases or infectious diseases consider the possibility of resistant infections when a patient is slow to respond to therapy, has HIV infection, or probable contact with patients with HIV disease, or has a record of previous treatment or poor compliance. We have a suitable isolation room with negative pressure ventilation, which has been required for one patient. Although the fears of untreatable tuberculosis have not become reality, the possibility has been an incentive to check that our tuberculosis control policies are implemented. In my view, early diagnosis of infection, thorough close contact tracing, and good follow-up on treatment, are the foundations of the past success against tuberculosis and are likely to be the key to further improvement. Because Oxfordshire has differed from national policy and has not offered routine BCG vaccination in secondary schools, we have been careful to monitor the incidence of tuberculosis and to apply the other control measures of case-finding, treatment and selective vaccination. There has been only one case of tuberculosis, amongst about 100,000 teenagers and young adults, which can be attributed to the cessation of routine BCG vaccination in Oxfordshire schools in 1981. Although we are open to proposals that routine BCG should be re-introduced to Oxfordshire schools, it can be argued that the resources now spent nationally on routine BCG vaccination in schools could be more effectively used on enhancing selective vaccination, contact tracing and compliance with treatment. Equally important, but needing more than the resources spent on routine vaccination in schools, are the conditions that facilitate the spread of tuberculosis (whether multi-drug resistant or not): poor housing, homelessness, unrecognised infection in hospitals and prisons. There is a danger that the publicity given to "super-bugs" will distract attention from the essential public health requirements.

12. Also arising from the fears about resistant tuberculosis is the recognition that the legislation on infectious disease must be modernised. The Public Health (Control of Infection) Act 1984 was largely a consolidation of laws that were written more than sixty years ago, long before the antibiotics era². Tuberculosis is considered to be one of the infectious diseases to which the Act applies. The Act gives power, subject to the courts, to a local authority to detain, in hospital, someone whose infectious disease might be a public health hazard. It does not empower treatment, and it is granted to bodies that do not own or operate any hospital facilities (when the law was written, local authorities built and ran the infectious disease hospitals). These powers in the Act are cumbersome to apply and have little practical value, so I would try not to use them in the local authorities for which I am the proper officer (medical). On ethical grounds, I think that they should be debated publicly if they are to remain in force. Preferably they should be replaced by powers that are more sensitive to human rights, recognise the benefits of treatment, and are held by health authorities, assuming that health authorities continue to have public health functions. Powers that enabled supervised treatment and care at home would be more humane and helpful than the present powers of detention in hospital.

13. The Public Health (Control of Infection) Act 1984 is so outdated as to be a hindrance in the surveillance of infection. The Act requires doctors to notify certain infections based on a clinical diagnosis. In modern times, microbiological evidence is more useful, and reporting systems based on laboratory results have been developed. The laboratory reporting systems are voluntary and give information from hospitals to the national Communicable Disease Surveillance Centre in London, or to the Scottish Centre of Infection and Environmental Health in Glasgow. This flow of information by-passes the district health authorities and local authorities, although some of the information is sent to them in parallel, as a voluntary unpaid activity. In Oxfordshire, the laboratories tell me about infections of public health significance, and I know that similar arrangements exist in some, but not all, health districts. The names, addresses and other personal information are treated as medical and confidential, but for some conditions, it would be in the public interest for the information to be available as a formally notified infectious disease. Multi-drug resistant tuberculosis is an example of an infection for which there should be a statutory duty for laboratories to report the infection directly to the local consultants in communicable disease. At present, the clinician looking after the patient may notify the first diagnosis of tuberculosis, but there is no formal requirement to report the further information about drug-resistance.

14. One awkward feature of the current voluntary laboratory reporting system is that it has no definite denominators below the national level. Epidemiology depends on rates of disease, the numbers of cases per defined population. Without rates, the observations at different times and different places cannot be compared. Under the present laboratory reporting system, there is no accepted local denominator. Numbers of specimens or numbers of patients admitted to the hospitals served by the laboratories are variously used on occasions when rates are important. We are developing regional sets of the laboratory surveillance data, which is a step towards local rates. But the basic requirement for community infection control is to relate infections to the resident population, which immediately gives rates which can be specific for demographic factors like age, sex and socio-economic status. Furthermore it assigns responsibility for control measures. Using the data on MRSA given above, the incidence of MRSA in Oxfordshire residents was 11/100,000 in 1994, 28/100,000 in 1995 and 57/100,000 in 1996. The incidence of MRSA infections in Oxfordshire nursing home residents is 2 per 1000 per year, as judged from new cases detected by microbiology for clinical purposes, but the prevalence of MRSA carriage is likely to be higher.

² Review of the Law on Infectious Disease Control. Department of Health 1989.

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15. *Salmonella* infections are a disease which is important to public health but is not formally notifiable, except as food-poisoning. As the term food-poisoning is imprecise (food-borne infection is more accurate), many salmonella infections are not formally notified. Although most salmonella infections are informally reported by laboratories to the consultants in communicable disease control, and thence to environmental health officers, the unofficial status of the information can hinder investigation. The difficulties with this unofficial information are more likely to occur in the investigation of apparently sporadic infection than in the management of obvious outbreaks. However, for public health to be successful, problems should be detected before they present as obvious outbreaks.

16. The significance of the above remarks about salmonella infections to antimicrobial resistance lies in two different aspects. To the public health physician, antimicrobial treatment for salmonellosis plays a very small part in the control of infection or the management of patients at home. Most people with gastro-enteritis due to salmonellosis recover without antibiotics. However in a small proportion of cases, the salmonella infection spreads from the bowel to the bloodstream (salmonella bacteraemia). When this occurs, antibiotic treatment is strongly indicated. If there is an increase in human infections with salmonellae resistant to medical antibiotics, treatments may fail and deaths occur. This has not happened in my experience, but the spread of multi-resistant *Salmonella typhimurium* is causing anxiety. If *Salmonella typhimurium* regains its former place as the commonest salmonella type causing human infection, or if its successor in the top place, *Salmonella enteritidis*, acquires substantial resistance to antibiotics, there will be medical problems.

17. To date, my interest in multi-resistant *Salmonella typhimurium* has been in resistance being a marker of a particular strain. With the focus given by such a marker, sometimes called an antibiogram, public health doctors and environmental health officers can look for connections between apparently sporadic cases. One example of this occurred this summer when we encountered *Salmonella typhimurium* U 302, which is resistant to antibiotics. Without the additional marker, the significance of these six cases might have been overlooked amidst the 222 other cases of salmonellosis in Oxfordshire this summer. However the fact that this type of salmonella is uncommon and the Oxfordshire isolates had a different antibiogram to strains found elsewhere, was an incentive to find a local source. Dr S Cohen, a specialist registrar working with me, persisted until she found the probable link between the cases: a butcher whose hams had several different outlets, including commercially prepared sandwiches. This is one small episode, but it points to the possibility that there are hidden outbreaks beneath the numerous sporadic cases, if only we could improve our surveillance methods to detect them. The consequences could be a stronger case for less contaminated meat, better clues to veterinary investigation centred on the likely sources and less need for consumers to practise surgical standards of hygiene.

18. My interest in streptococcal diseases began with research into rheumatic fever and acute post-streptococcal glomerulonephritis. These diseases are still relatively common in developing countries, and the sensitivity of Group A streptococci to penicillin is important in the prevention of rheumatic fever. In Britain, *Streptococcus pneumoniae* is the commonest streptococcal disease to cause death or admission to hospital, most commonly by pneumonia, but also by bacterial meningitis. *Streptococcus pneumoniae* is becoming more resistant to penicillin and erythromycin. In Britain in 1994, 2.5 per cent of strains were resistant to penicillin and 11.2 per cent resistant to erythromycin.³ This has not caused clinical problems in my experience, but it is sometimes given as a reason for promoting the use of pneumococcal vaccine. Even without the factor of antibiotic resistance, there is a good case for offering pneumococcal vaccine to people who have medical conditions that place them at increased risk of severe pneumococcal infections.

19. It is likely that the prevalence of antibiotic resistance in common respiratory pathogens, like streptococci, is related to the amount of antibiotic used in primary care. The relatively low prevalence of penicillin resistant *Streptococcus pneumoniae* in Britain may be due to the conservative use of antibiotics in British general practice, and the restriction of keeping antibiotics as prescription-only medicines. The rates of erythromycin resistance in streptococci appear to be related to the popularity of macrolide antibiotics.

20. Another bacterium that is normally present in the respiratory tract, but can cause severe invasive disease, is *Neisseria meningitidis*. This cause of meningitis and septicaemia is rightly feared by parents and doctors, and is generally perceived as a public health problem. Until the development of meningococcal vaccines for children is complete, secondary prevention by antimicrobial drugs to prevent further spread amongst close contacts is one of the few preventive measures available. Until 15 years ago, sulphonamides, particularly sulphadiazine, was used for this purpose. The increasing resistance to sulphadiazine has forced us to change to rifampicin, which is as effective, but has a greater risk of side-effects. It is hoped that resistance to rifampicin does not become common before the paediatric vaccines are in use. This concern is not speculative, because the demand for rifampicin prophylaxis whenever there is publicity about meningitis runs a risk of inducing resistance. It is also worth bearing in mind that the very effective vaccines against *Haemophilus influenzae* type b, a cause of bacterial meningitis in small children, came into routine use at the point when resistance in this bacterium to ampicillin and chloramphenicol was becoming a threat to successful antibiotic treatment.

21. It is sometimes said that the newer cephalosporin antibiotics, like cefotaxime, which are good choices for treating bacterial meningitis, have lessened the threat of antibiotic resistance in the bacteria that cause

³ Anon. Antimicrobial resistance of pneumococci isolated from blood and cerebrospinal fluid 1993 and 1994. Communicable Disease Report 1995; 5:187-8.

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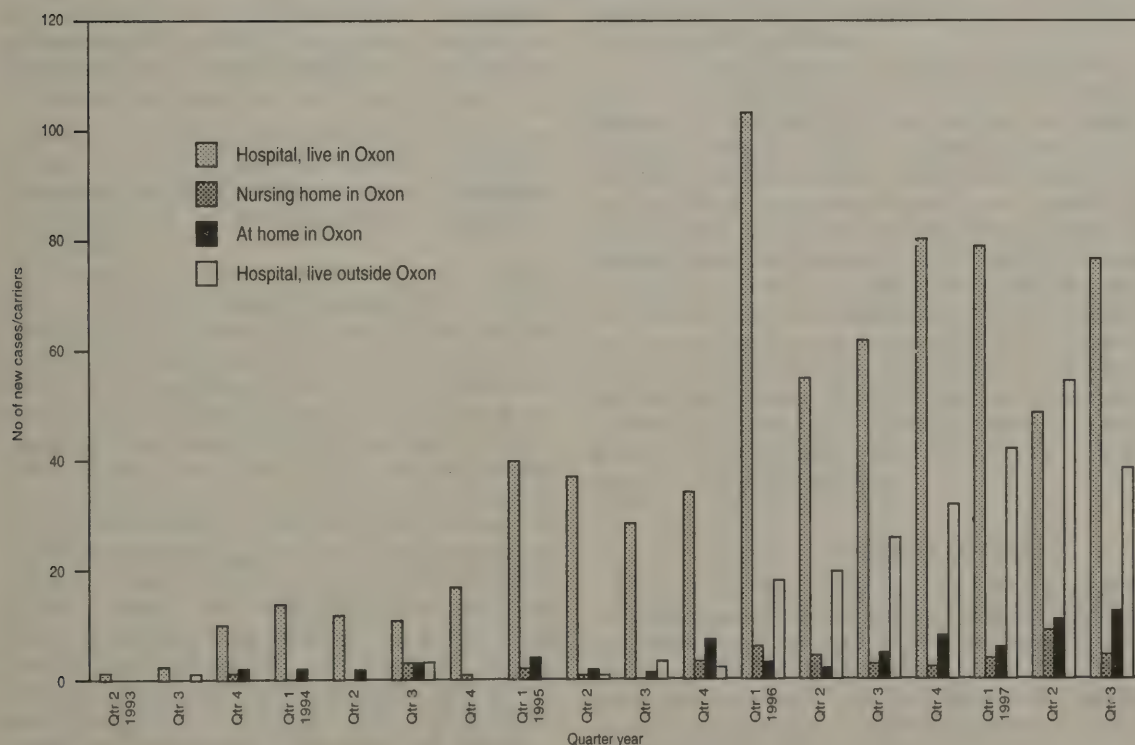
meningitis. Such a view overlooks the problems in poorer countries, where resistance to the cheaper antimicrobial drugs, like penicillin, sulphonamides and chloramphenicol is a public health issue.

22. There is a general assumption, which I share, that it is right to try to control the use of antibiotics in general practice. Certainly, there is interest amongst general practitioners in containing prescribing costs. With this in mind, Oxfordshire Health Authority has guidelines for antibiotic use in general practice. The intention is the same as a hospital antibiotic policy, but the independent status of general practice means the document is guidance, not policy. The guidance recommends first choices of antimicrobials (chosen to be effective, safe and inexpensive) for various clinical types of infection, recognising that treatment will be started without microbiological results.

23. From the information about prescribing in general practice in Oxfordshire, we have observed wide variations in the use of the more expensive antibiotics, which would be second line drugs in our local guidance. Figure 2 shows data on ciprofloxacin usage in Oxfordshire practices in 1996, when nearly £200,000 was spent on ciprofloxacin, making it one of the top ten drug costs in general practice. The use of these antibiotics is commented on in the regular newsletter that we send to the primary care teams, and may be discussed with individual practices during the visits by the medical adviser. We are at an early stage of our programme to improve antibiotic usage in the community and we need to examine the efficacy of guidelines and prescription monitoring. This is another field in which standardisation would help in comparisons and evaluation.

24. Finally, I am aware of the interest in vancomycin resistant enterococci, and the possibility that growth promoters in animal feeds may encourage the evolution of resistance. To date, the very few infections caused by vancomycin resistant enterococci in this region have been detected in hospital, and have not caused any problems in the community. This point summarises my experience of antimicrobial resistance in public health: it is a matter of real concern, it must be monitored efficiently, but so far antimicrobial resistance has not had much impact on the incidence of disease arising outside hospital.

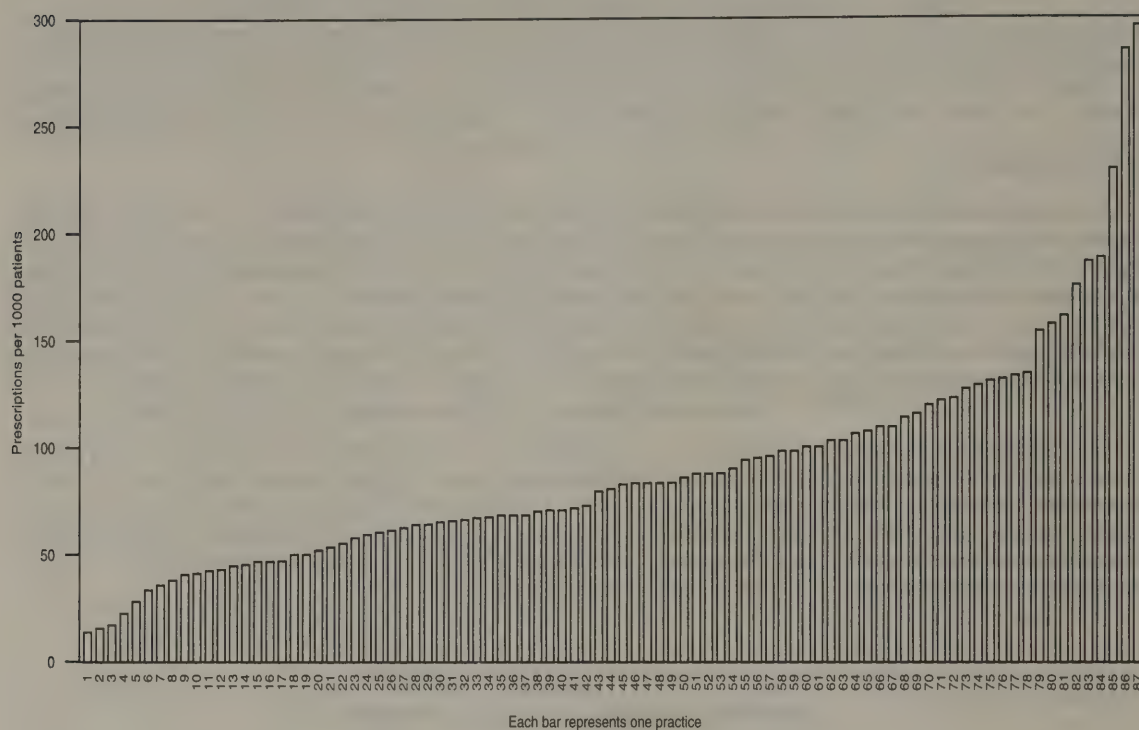
Figure 1
MRSA in Oxfordshire, with the probable place of acquisition



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Figure 2
Ciprofloxacin prescriptions per 1000 prescribing units
(a standardisation of the number of patients on the GPs' lists, adjusted for age) in 1996 in Oxon.



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Examination of witness

DR RICHARD MAYON-WHITE, Regional Epidemiologist and Consultant in Communicable Disease Control, Oxfordshire Health Authority, was called in and examined.

Chairman

148(A). Dr Mayon-White, thank you very much for coming to see us today. Perhaps you would like to introduce yourself and then give us an account of your work for the Oxfordshire Health Authority.

(Dr Mayon-White) My Lord Chairman, thank you for inviting me. I work as a consultant in communicable disease control for Oxfordshire Health Authority and in that position my responsibilities are to detect and to control any outbreaks that might occur in the county of Oxfordshire, to advise the health authority, the county council and the five district councils in Oxfordshire, on infection control matters. I run a surveillance system to measure the incidence of infectious diseases. My remit extends to some non-communicable disease problems related to environmental pollution and chemical incidents. I have a responsibility as the infection control doctor to the community health trust, and that extends to advice to nursing homes, residential homes and schools. Therefore, it is a broad remit picture in the county of Oxfordshire. I have a role as senior lecturer in the University of Oxford in teaching in public health and that gives me, of course, a lot of interest in research and teaching; and I also act as a regional epidemiologist covering the four counties of Northamptonshire, Buckinghamshire, Berkshire and Oxfordshire and that gives me a broader picture.

149(A). Which in your opinion are the resistant organisms which cause the main problems in **community acquired infections** and which organisms are most prone to spread between hospital and community?

A. Methicillin resistant *Staphylococcus aureus*, MRSA, is the top for several reasons. One is its high prevalence: it is common. It is causing problems and difficulties. At the moment, I think it is in a position where we are not clear whether we can control it or not, despite its frequency. Not all methicillin resistant *Staphylococcus aureus* infections are very serious—some of them are almost trivial, one might say, particularly at the level of colonisation. Multi drug resistant tuberculosis is more threatening, because we rely on antimicrobial treatment to control tuberculosis, not only in the individual but also to prevent further spread. I foresee there being further problems in the future if the common respiratory organisms like *Streptococcus pneumoniae*, which is the common cause of pneumonia, become much more resistant to antibiotics, particularly penicillin. Then I think that we would have real problems in managing pneumonia.

150. And enteric organisms?

A. Enteric organisms, my Lord Chairman, I see as being an unknown threat and my experience with infectious diseases is that the unknown threats are disturbing because they can happen. Just because they have not occurred yet does not mean to say that they will not present new problems. I am concerned that if

we get multiple antibiotic resistant enteric pathogens spreading, then I am not sure that we know how to manage that problem. I do not think that we have got much experience of how to cope with it.

151. That does raise the question of the relative contribution to these **infections from non-human sources** such as animals and the food chain. Would you like to comment on that?

A. My Lord Chairman, the main problem now is the organisms that have their origin (reservoir) and method of spread through human beings rather than coming from animal sources. So, talking in a day-to-day practical way, what I have got to do today, this year, next year, has got to be about the organisms that have this human origin. But I am worried about what may emerge from animal sources in the future, particularly as I think that we have not adequately controlled the spread of salmonella into human foods to cause human disease.

Baroness Masham of Ilton

152. Does your remit cover **prisons** and the spread of infection coming in and out of prison? It has not happened here yet, but in Spain there is a big problem of tuberculosis in prisons.

A. My Lord Chairman, I am glad that that question has been asked because prisons are, to my way of thinking, a problem for us working in health authorities because we have no direct responsibilities for health within prisons. People like myself are involved when there are problems with infection in prison. I will go in, help and advise, but I have no authority there and I have to work through the prison medical service. This is normally not a difficulty, but it is not the same organisation (the NHS) as I work for. I would like there to be a standard which applied to the whole country, regardless of who is providing the medical service. There should be a common standard, preferably using common resources, so that it does not really matter where the infection is, it is managed as a corporate effort.

Baroness McFarlane of Llandaff

153. Would you please describe infection control in the community, the staff who are involved and what their roles are? How widespread is the establishment of **community infection control teams**—and your paragraph 6 referred to this—across the United Kingdom and are they cost effective and what are the main obstacles to effective control?

A. My Lord Chairman, community infection control has, very like hospital infection control, a core team usually made up of a medical person and a nursing person. The title of the medical person is the Consultant in Communicable Disease Control—CCDC—and the title of the infection control nurse is the Community Infection Control Nurse—CICN. That

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DR RICHARD MAYON-WHITE

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[Baroness McFarlane of Llandaff *Contd*]

is the core professional team. I believe that they should be supported by somebody who has got data processing skills (an information officer for want of a better word) and adequate secretarial and administrative support. Their functions would be to advise those people who are managing institutions that provide community care. The institutions extend from community hospitals (general practitioner or cottage hospitals) through nursing homes and residential homes to boarding schools. These institutions, plus the primary health care teams (general practitioners, district nurses, practice nurses, health visitors) plus anybody outside hospital who wants advice, which may be a company with some infection problems. In addition to advice, its functions include the investigation of outbreaks, and writing policies and codes of practice for those organisations so that they can run their own affairs with good infection control.

Chairman

154. In that respect where do you see the work of the CCDC in the administrative structure of the health service, at what level would you wish to see him or her operating?

A. My Lord Chairman, consultants in communicable disease control, under the present arrangements, are appointed by district health authorities so they cover something between 250,000 and one million people; the typical population is round about half a million people. Most districts have one consultant, a few of the larger districts have two. With the present structure of the health service, health authorities are the right placement for the time being. There are some reasons for a big metropolis to have a combined service that covers all its health districts—Birmingham and Manchester have such arrangements. Out in the shire counties, it seems that the county boundary or health authority boundary is about the right size and shape.

Baroness McFarlane of Llandaff

155. But you were saying in paragraph 6 of your paper that some districts in fact do not have infection control nurses. How widespread is that?

A. There are about 20 per cent of districts who have yet to appoint a community infection control nurse. I think that many of them would appoint as soon as resources allow. There are still, I am afraid, a few districts where the consultant post is not filled; it is temporarily filled by a locum or with some unusual arrangement, while they are looking for a consultant.

156. And is the main lack therefore their educational role or would it go wider than that?

A. I think that it is to do with the status of the job, and the interest in public health as a career. If you are an infection control nurse, I would think that it is more attractive to work in a big hospital. It is simpler to work in a big hospital where you have one organised structure, and you know the limit to your work.

Community work is protean because it keeps changing its shape and activity.

Baroness Masham of Ilton

157. Having been at a conference I heard some nurses saying that they felt very isolated as infection control nurses. Is that true?

A. I think that is true, but the nurses who are going to follow me with their evidence can speak for themselves. It applies in hospital, even more to the community infection control nurses because they may be the only staff working as nurses within the health authorities. Where people recognise isolation to be a problem, you can address it, you can build bridges, you can have professional support and leadership coming from a practising nurse so that they do not feel isolated.

Lord Dixon-Smith

158. Dr Mayon-White, what is your experience of the impact of **general practitioner education** on prescribing patterns and antibiotic usage? Obviously this is a continuing process. Secondly, are there commercial pressures involved in that education?

A. My Lord Chairman, I think that education for general practitioners does make a difference in their prescribing patterns. Quite a lot of my evidence to you has necessarily been limited to my own experience and so I am only speaking for Oxfordshire which I know well. We have noticed that the teaching and training practices tend to prescribe less of the expensive antibiotics—and, indeed, fewer antibiotics overall—than the non-teaching, non-training practices. It is not a very big difference, but the extremes are not so wide: particularly, you do not find very high prescribers in the practices that contain training and teaching doctors. This is an indirect answer to your question, but it does show, to my way of thinking, the important influence that comes from the educational process: if you are teaching others, you get taught yourself. Therefore, my Lord Chairman, I think influence of an educational nature is important in general practice prescribing. I have no doubt that the commercial activities of the pharmaceutical companies are another important influence. Sometimes it is to the good, where it can be a collaborative process in setting policies, and getting educational messages across. However, I think that the health authorities, the general practitioners themselves, hospital specialists who have got good knowledge, have to be in control of the process, otherwise the activities of the pharmaceutical representatives are simply to promote their own companies' products.

Lord Porter of Luddenham

159. Is there a role in **education on antibiotic usage for patients and the public**?

A. I believe that there is. My understanding is that what general practitioners prescribe is affected by what the doctor knows and believes, and what the patient knows and believes. When these two coincide, you get the best result, that is, the most satisfied patient and the

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DR RICHARD MAYON-WHITE

[Continued]

[Lord Porter of Luddenham *Contd*]

best use of prescribing. Where there is a divergence, particularly if the general practitioner is using knowledge and information that is not available to the patient, you still may get a good outcome but the patient does not feel satisfied. There is a very important role in educating the patients not to expect an antibiotic for every infection that they present with, particularly as there is very good evidence that most of the minor community acquired infections recover by themselves and do not depend upon antibiotics.

160. And how could this educational process of the public best be achieved?

A. In many different ways, my Lord Chairman. It begins in school, learning what to expect of health services (partly citizenship, partly biology).

Baroness Platt of Writtle

161. What about a school nurse? Would a school nurse do that?

A. My Lord Chairman, school health nurses do have an important health education role, but I suspect that they do not have enough time because most of them cover several schools, and there are more important things for them to tackle, particularly sexual health and drug related misuse matters.

Lord Porter of Luddenham

162. And would teachers be able to carry this out?

A. No, I do not think that teachers would without help.

163. So who would do it?

A. What we should seek is that the health education departments working for health authorities, often with a contract, will prepare educational material to be used in schools which would be available to school nurses and teachers. However, that is only a small part of it. I think that we cannot wait for a generation of school children to grow up to the age when they are older and when they are the main consumers of medical care and antibiotics. There must be an adult educational programme, working as it does with so many health things, through magazines, radio, television, newspapers.

Baroness Platt of Writtle

164. Dr Mayon-White, looking at figure 2 in your paper, how can you explain the large variations in the **prescribing practice of general practitioners**?

A. I think that both ends of the spectrum need attention, my Lord Chairman; including the doctors who are using very few antibiotics who may have missed an educational message. The concern with expenditure in health care puts all the attention at the other end, those who are heavy users of expensive drugs. The normal process is that the heavy usage is noted by the medical adviser of the health authority, (typically an ex-general practitioner) who, in his or her visits to the practice, will prompt comment and questions. For example, saying, "You are using rather a lot more ciprofloxacin than most other practices.

What is the thinking here?". They may say, "Well, actually it is marvellous, it cures all the problems that we see our patients presenting with and therefore we are going to go on prescribing it"; or they may say, "That is interesting. Maybe we were more influenced by the advertising, maybe we need to rein it back". Most general practitioners are interested in controlling their prescribing costs.

165. Also there is the question of the development of resistance as a result of over-prescribing, is there not?

A. Yes, there is. Whether that is specifically linked to new and expensive drugs or not, I do not know. I think that you might have to ask other people who have got more knowledge and who have gone further than I have done in the use of particular antibiotics, particularly the cephalosporins, and see whether that is producing resistance in general practice.

Lord Dixon-Smith

166. Can you express a view as to whether there is a general awareness among general practitioners of the potential problems of resistance?

A. My Lord Chairman, I think that it is not a well recognised problem and this is not confined to general practitioners; it applies across the medical profession.

Lord Walton of Detchant

167. There has been a great deal of interest in the last few years in the so-called toxic shock syndrome in association with *Staphylococcus aureus* infection. Is there any evidence that that is more common in infections with a resistant organism or are the two unrelated?

A. My Lord Chairman, to my knowledge they are unrelated and, as a more general point, **infections due to the resistant organisms tend to be no more severe** than those due to the more sensitive organisms. There has been some discussion on whether that is still the case with methicillin resistant *Staphylococcus aureus*, but I think that in general terms it is no more virulent.

168. You have called for a **national strategy for the control of methicillin resistant *Staphylococcus aureus***. What sort of strategy do you have in mind, and do you have any possible estimate of the cost of implementing such a strategy?

A. My Lord Chairman, what I have in mind with a strategy for the control of methicillin resistant *Staphylococcus aureus* is as follows. We have national guidance and yet it is variously interpreted in different hospitals in different places according to the circumstances. There seems to be no objective for what we are trying to achieve in the control of methicillin resistant *Staphylococcus aureus*: are we trying to eradicate it or are we trying to keep it down? I think that it is too late to eradicate it because we are dealing with something that is endemic. When we are dealing with endemic problems you need more than guidance, you need a strategy which has a target, so I would begin by setting objectives. What I want is to reduce the number of outbreaks per hospital. I would

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DR RICHARD MAYON-WHITE

[Continued]

[Lord Walton of Detchant *Contd*]

like to reduce the prevalence of methicillin resistant *Staphylococcus aureus* in the population, particularly in the nursing homes, and I want to reduce the number of new infections in hospitals. These require measurements that, in some way, can be compared from place to place. Supporting that objective, I would want more authority given to the guidance so that it becomes a national policy. To operate a strategy, I would have a task force which draws upon the national expertise. The task force would be for a finite period of time—five years—and its objective would be to bring down the rates of infection.

169. May I just follow up that point by asking you whether you personally have come across vancomycin resistance—VRSA—in this country? We know that it is developing in Japan and in other parts of the world.

A. No, my Lord Chairman, as far as I know it is not present. You did also ask me about the cost of the strategy. It is very difficult to work out the cost. That would be one of the incidental byproducts of trying to operate a strategy. Taking the expenditure in Kettering, as an example of the cost of managing endemic MRSA, where they spent £300,000 in a year, and if you multiply that by 200 then we are talking about £60 million being spent on the control of methicillin resistant *Staphylococcus aureus* in the United Kingdom. Now that is a very “back of the envelope” type of calculation, but it would seem to me that the cost of the strategy that I was proposing was very small in relation to that level of expenditure.

Baroness Masham of Ilton

170. My Lord Chairman, may I just go back for a second to the public and education and also the control for meningitis. Where I live in north Yorkshire there have been some really tragic cases and the public are very aware of the dangers of meningitis. General practitioners have missed it perhaps, and it is tragic. Do you think that there should be a **strategy for the control of meningitis** because the schools are devastated. Just a couple of weeks ago it happened with a 12 year old boy and it happened with a baby of a friend of ours.

A. My Lord Chairman, I think that we are closer to having a strategy for the control of meningitis. Meningitis is relevant when we are talking about antimicrobial resistance because we saw in the past the growth of antimicrobial resistance in *Haemophilus influenzae*, when it was the commonest cause of bacterial meningitis. We have the increase in antibiotic resistance in the *Streptococcus pneumoniae* (the pneumococcus) which is, after the meningococcus, the second most common bacterial cause of meningitis. We are closer to having a national strategy for the control of meningitis because we have guidelines and policies which are followed pretty closely in every district. This contrasts with what I said about MRSA. Secondly, my Lord Chairman, we have a programme of developing vaccines so that there is, in the future, a target when we will finally control meningitis. Thirdly, particularly the two charities which are associated with meningococcal disease, the National Meningitis Trust

and the Meningitis Research Foundation, have had a very good programme aimed at public education, which has fitted well with the public health work done by the Department of Health and district health authorities. However, the problems with meningitis are that it is not easy to recognise all cases in time to make a real difference with antibiotic treatment. That is why we have the tragedies that you have referred to.

Lord Gregson

171. Can you tell us what are the most effective ways to encourage or enforce the “**basic hygiene practices**” that are listed in paragraph 10 of your paper? At the same time would you please comment on the effectiveness of training and contracting and the significance of staffing levels and resources, certainly in view of the emphasis that this Government are putting on care in the community, which I believe broadens the whole subject?

A. My Lord Chairman, I think basic hygiene is essentially good practice. The problem is that it is so easy to slip into bad habits if you do not have middle management which is totally committed to running an institution in a good, disciplined way. One of the things that I have seen within the health service is the loss of middle managers who have worked in clinical practice and gained experience, authority and respect of staff. So often one finds relatively inexperienced managers working on their own with other very inexperienced people, without strong examples of keeping good hygiene. Good hygiene is not very complicated: it is about washing hands, keeping places clean, serving safe food, making sure that food is not stored under the wrong conditions, that rooms are well ventilated, that the laundry gets done at the proper time and so on, very simple things, a bit boring to do, and that is one of the reasons why, from time to time, they slip. Basic hygiene relies on services that are often contracted out by the organisation that runs the hospital. If you are trying to save money, it is easy to go on paring away at the quality of the service until suddenly you realise that you have got poor quality, that basic hygiene has been lost, and then you have got to start all over again. It may take five years to restore standards.

Lord Walton of Detchant

172. Do purchasers take enough account of the significance of resistant infections? I know that the Infection Control Nurses Association who will follow you in giving evidence said that most infection control teams have no formal contracting arrangements with their purchasers and that most infection control teams in hospital trusts have no budgets. What practical difference would it make if infection control teams had their own **contracts and budgets**?

A. My Lord Chairman, if I may begin with the first question, which was, do purchasers take proper account of antimicrobial resistance in their decisions. For most purchasers, the main problem is keeping services going with the money that they have got, so it has to be a financially dominated agenda for most

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DR RICHARD MAYON-WHITE

[Continued]

[Lord Walton of Detchant *Contd*]

of the time. There are pressures to give new therapies and, more of the existing therapies; because of that, worries about antimicrobial resistance tend to come far down the agenda. They should not. An approach that I would advocate, my Lord Chairman, is that in the basic contract between purchasers and providers, there has to be compliance with national standards and guidance. Then what we need are national standards and national guidance which set good policies for hospital management. You do not need specific contracts between health authorities and infection control teams, if the basic contract between a purchaser and a hospital or a community care service sets high standards of infection control. Whether it helps an infection control team to have its own budget or not, will vary from team to team. It depends how good a team is at managing a budget or whether it is more efficient to have its budget managed by somebody who has got the appropriate skills so that the team can concentrate with the tasks for which they are professionally trained.

Lord Porter of Luddenham

173. Dr Mayon-White, what do you see as the agenda for **research** in this field of infection control in the community?

A. My Lord Chairman, the research that I would like to see done begins with some formal trials of control measures. At the moment we are using best advice and existing practice, and trying to assess whether they are right. I do not think that there is any escape from having to do formal trials of control policies, if we wish to learn more. Such studies are very difficult: I make no pretence about that, because it would mean changing practice in a number of places. The second thing is that we need much better information about the prevalence of antimicrobial resistant organisms in the community. The difficulty with this is that it tends to fall down between two stools of normal practice, and strict research. We should recognise this epidemiology as development which needs to be strengthened and funded. The development that I am referring to, my Lord Chairman, is the collection of comparable data on antimicrobial resistance in a number of different settings across the country. That may enable us to draw lessons of which control policies are more effective than the others, but I suspect that you need more formal trials to find some of the answers.

174. Is funding inhibiting the progress?

A. It is a difficulty, for the reasons that I have said. Where people have proposed and proceeded to collect data in standardised form to the quality that I would expect in research, they have been told, "That is not really research, that should be part of the basic service funding", and they go round and round in circles looking for money.

Chairman

175. Dr Mayon-White, we have heard this comment before from other people that the type of research that you are referring to is not "sexy" enough

to interest the research councils. Would you agree with that?

A. My Lord Chairman, yes, I would agree with that. I think that is what the research and development budget in the National Health Service is for, in part. You might to call it "health services research", which is a bit sexier.

Lord Gregson

176. You do have in Oxford, of course, one of the centres of excellence in the type of activity that you are talking about, Richard Doll's activities in epidemiology; and, of course, you have got the Oxford Unit and the Radcliffe, so you have got a tremendous potential to influence the direction of that type of research?

A. My Lord Chairman, what Lord Gregson says is very true, and it is important to unlock that potential to the problems that we are addressing here.

Lord Dixon-Smith

177. How could the epidemiological information available to you regarding antibiotic resistant infections in the community be improved? Do you see investment in information technology as a priority?

A. My Lord Chairman, the answer to the second question is that information technology is available and it is making a difference, and will make more of a difference with more investment. However, to go to the first question, the problem is several fold. One factor is, as I have said in my evidence to you, that the **regulations** about reporting infections are out of date. The regulations refer to diseases by the terms that they were known by nearly a century ago. We should be using the information that is available from microbiology laboratories to identify infections by their causative organisms. I believe that the microbiological diagnosis needs now to fall into the legal framework of formal notification. That would mean laboratories reporting to the local consultant in communicable disease control the infections that have public health importance. This is done informally at the present time, and it strains slightly the rules of medical confidentiality. Sometimes general practitioners and hospital doctors will object, but I think that in most cases people realise that the sharing of information is in the public's interest and should be done. However, it would be very good to have that law revised and brought up to date. It would immediately cut through some of the delays in implementing the electronic transfer of information. Much of the laboratory data is already on computer. Most of the health authorities are sufficiently computerised to receive the data. At the present time, because it is not a formal system, we are using the voluntary reporting system from laboratories to the Communicable Disease Surveillance Centre, which goes through regional epidemiologists to the surveillance centre in Colindale. If we used standard electronic systems across the country, there would be no difficulty in sending the data centrally for surveillance purposes

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[Continued]

[Lord Dixon-Smith Contd]

and locally for control purposes. It is a matter of using the tools that we already have.

178. So a solid legislative background would provide the impetus and, more importantly perhaps, overcome some of the potential ethical argument?

A. Yes, it would indeed.

Baroness Masham of Ilton

179. Which of the important conditions, infections, diseases, are not formally notifiable?

A. Let us begin with the ones that I have already mentioned. Methicillin resistant *Staphylococcus aureus* infection is not notifiable. In fact, it comes nowhere near being a notifiable infection and you cannot stretch any of the existing definitions.

180. And that would bring the general practitioners in too?

A. Yes. Secondly, there is Legionnaire's disease.

181. It is not notifiable?

A. No, it is not. Nor are any of the intestinal infections, which can be food borne infections, notifiable when they are not food borne. I cannot think of any way in which they could be strictly notifiable under existing legislation.

182. They are notifiable if they are food borne?

A. Yes.

183. Salmonella, for instance?

A. Salmonella, if it is identified as food poisoning, is notifiable, but it is the food poisoning that is notifiable. But salmonellosis is not a notifiable infection per se. The food poisoning statistics are a ragbag of conditions. Where a general practitioner thinks that a patient's diarrhoea and vomiting after a take-away meal the night before is food poisoning, the illness is counted as food poisoning, mixed with proven infections by *E.coli* 0157, salmonella, etc.

184. What about tuberculosis?

A. TB is a notifiable infection and that is important because some of the control measures really only can be applied if something is formally notified.

Baroness Platt of Writtle

185. Dr Mayon-White, you point out that the statutory powers of detention are out of date in paragraph 12 of your paper. Should they be brought into line with modern medical practice and organisation or could they simply be dispensed with?

A. My Lord Chairman, my understanding is that many public health doctors would be unhappy to totally dispense with the powers of control over someone who might be spreading multidrug resistant tuberculosis. There needs to be some means of preventing such a person walking around freely into places perhaps with children and spreading the infection there. At the present time the legislation enables me, if a court agrees, to restrict a person from going to work or to school, so there is protection. It also says that I can keep somebody in hospital but I cannot treat them. Detention in hospital makes me very

uncomfortable for several reasons. The detention of people is not a hospital function. The prison service exists for the detention of people, but a patient would have to be an extreme risk before people would agree that it was a criminal activity that such a patient was not observing control measures. What I would press for is supervision at home with treatment, to replace detention. I hope that I would be able to persuade most of my professional colleagues that that was an adequate measure.

186. And that would also involve education of the other people who are dealing with that person presumably?

A. It would indeed, but I see much less difficulty than you might expect. The most vulnerable people are homeless. The staff providing community care for homeless people are so dedicated that they pick up the education on health matters very quickly.

187. The other problem from reading the evidence that we are going to have next this morning, is the feelings of **the nurse who found that she had been infected**, and I found that very interesting because that obviously makes a very difficult relationship with the patient, I would have thought?

A. Is the question about tuberculosis or about methicillin resistant *Staphylococcus aureus*? If we were talking about tuberculosis, which is a better example to consider, I have been involved in the care of doctors who have had tuberculosis that they probably acquired in the course of their work. They are very concerned about the risk to their patients. Looking at it dispassionately, the good that doctors do in their work completely outweighs a small unavoidable part in the spread of infection.

188. But it is important that they should be persuaded of that, I imagine?

A. Indeed, my Lord Chairman, and it is important that people who are working in the health service understand that they are more vulnerable to infection than others.

Lord Gregson

189. Should we not be taking some cognizance of the New York experience with treating tuberculosis where they now have compulsory treatment and you can get a court order in New York to say that someone must be compulsorily treated? I know that we have not yet got that degree of resistant TB in this country, but it is more likely to arrive here at some stage, is it not?

A. Yes, that would be an example of what I was referring to by supervised treatment at home.

190. But this is compulsory, of course.

A. Yes.

191. That is the important aspect of it. If you just simply supervise it, these people disappear, of course. That was the point.

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[Continued]

[Lord Gregson Contd]

A. I am sorry, my Lord Chairman, I should have made it clearer that I was talking about compulsory supervision and not voluntary supervision.

Baroness Masham of Ilton

192. My Lord Chairman, if I may come in here, have we enough special rooms for the treatment of resistant tuberculosis in the hospitals?

A. Most hospitals will know, if they have not got facilities themselves, which hospitals that are reasonably close to them do have such facilities. One of the questions that you might have asked me, my Lord Chairman is, what should you be looking to when you visit hospitals.

Chairman

193. We will be coming to that shortly.

A. I would suggest that you look for rooms which are used for isolation for all patients, not only patients with multidrug resistant tuberculosis, and see what you think about them as being the right conditions and whether they are appropriate.

Baroness Masham of Ilton

194. We do not have to look very far, just across the river with that case of tuberculosis and the HIV patient.

A. My Lord Chairman, St Thomas' Hospital across the river, which trained me, is well resourced compared with many hospitals.

Lord Porter of Luddenham

195. You have referred to a number of diseases which are not reported. In paragraph 13 of your paper you talk about **putting laboratory reporting on a statutory basis**. I wonder how far you go with this, which pathogens and resistance patterns should be required to be reported?

A. The number of resistant organisms which would be made reportable from laboratories would be methicillin resistant *Staphylococcus aureus*, multidrug resistant tuberculosis, vancomycin resistant enterococci and resistant pneumococci. The reason that I would keep the list short is that I would want the information that an organism is resistant to antimicrobials to be consistent and reliable, and that may mean that the laboratory has to do rather more than routine antimicrobial testing for clinical management.

Chairman

196. We are going to **King's College Hospital** next week. Can you advise us as to what we should be on the look-out for?

A. My Lord Chairman, I have already suggested that you look at the isolation facilities. If you are on the wards, ask which patients have been there for a long time, ask whether they have got a hospital acquired infection, and whether that is the reason that they have stayed. It is worth looking at some of the basic hygiene measures that I have alluded to, asking staff whether they are trained in infection control and whether, when they started work in that ward and that hospital, they were told of the arrangements that apply in that hospital. I hope that you will not be shown areas that are not clean, but if you looked hard enough or made an unannounced visit, you probably would. Most of all, my Lord Chairman, I would look for overcrowding. At the beginning, we were talking about infection. The main problem with antimicrobial infections today is the spread of human pathogens which depend on crowding people together. I think we have observed that when hospitals are over-full, the standards of hygiene fall and the rates of spread of infection rise.

197. And finally, Dr Mayon-White, a small group of us are going over to the **United States** to see what they do there. What should we be on the look out for and what do you think are the sorts of lessons that we might learn from the USA that are pertinent to this country?

A. My Lord Chairman, what impressed me from the United States has been their commitment to epidemiology, their national policy and guidance which seem to be much more clear cut, often introduced years before this country, and with a greater commitment to the raising of standards. It would be very interesting to hear how federal policy fits with the greater autonomy of the states and individual hospitals. Does it really work, and is it followed through?

198. We have heard that information technology plays an important role in all aspects of public health surveillance in the United States. Is that so from your experience?

A. It is, my Lord Chairman, from what I can tell, although the system of laboratory reporting to the Communicable Disease Surveillance Centre in Colindale is in advance of other countries. I think that the quality of some of the antimicrobial data in Britain is better than you will find in most other countries. So that I would want to keep the good things that we have got.

199. Dr Mayon-White, thank you very much indeed for coming along.

A. Thank you, my Lord Chairman.

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1. INTRODUCTION

1.1 The Infection Control Nurses Association (ICNA) welcomes the opportunity to provide evidence in writing, in person, in public and on the record to the 1 House of Lords Inquiry into the resistance of antimicrobial agents.

Given the skills, knowledge and expertise of our members, the ICNA has agreed to focus on specific aspects of the Inquiry and to address these issues from the nursing perspective whilst recognising the importance of the multidisciplinary infection control committee and in particular, our professional relationship with our medical microbiologist colleagues.

1.2 Our evidence will focus on section (i) of the Call for Evidence. This section covers:

“bacterial resistant to antibiotics: e.g., TB, pneumonia, meningitis, salmonella, gonorrhoea and hospital infections inc. MRSA. Extent and trends; surveillance; infection control.”

1.3 Our evidence will relate specifically to:

MRSA—hospital and community perspectives

Vancomycin resistant enterococci

Aminoglycoside resistance

Multi-drug resistant TB (MDRTB)

1.4 In summary, our evidence will focus on the impact of antimicrobial resistance *per se* and in particular on issues relating to:

patient management

strategic management

infection control management arrangements

2. INFECTION CONTROL NURSES ASSOCIATION (ICNA)

2.1 The Infection Control Nurses Association was founded in 1970 and has a current membership of approximately 900 representing the vast majority of infection control nurses (ICNs) currently employed in the UK. The Association is a registered charity and consists of 11 regional groups (covering Ireland, Scotland, Wales and eight English groups) and is administered by a National Executive Committee comprising representatives of all 11 regional groups together with three elected executive officers—chairman, treasurer and secretary. All

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posts are honorary and all executive officers and others give their services free and in their own (and occasionally their Trusts) time.

2.2 There are five categories of membership—full, associate, commercial, overseas and honorary. Full members of the Association are those who are wholly employed in the specialism of infection control either in hospitals or the community.

2.3 Infection control nurses are all registered nurses the vast majority of whom are registered at level 1 (general nursing) with the UKCC.

2.4 To practise as a clinical nurse specialist, ICNs will have undertaken a post-basic professional qualification. Most of them have undertaken a specific certificate or diploma in infection control. A significant (and increasing number) of ICNs are undertaking either first or higher degrees in infection control, health policy, business administration, nursing or public health.

2.5 The development of the ICN as a specialist nurse should be underpinned by sound management experience in a clinical setting. The majority of ICNs have entered infection control with a minimum of four years post-registration experience, most having experience at ward sister/charge nurse level.

2.6 As one of the core components of the ICN role is education and training, a post-basic teaching qualification (such as ENB 998 or City and Guilds 730) is recommended. Indeed ICNs teaching as specialists within academic institutions such as schools of nursing must now show evidence of a recordable teaching qualification.

2.7 The ICNA contributes to the continuing professional and educational development of its members by holding an annual educational conference held over three days in September. This conference is also the major source of income into the Association as it is well supported by a large, high quality commercial exhibition.

2.8 The ICNA, through its well developed infra-structure and emphasis on communication (both within and outwith the organisation) has positioned itself to be able to respond promptly and comprehensively to requests for members' expertise. The Association's members are increasingly asked to serve on expert groups at a national level and our Association is widely recognised by our medical microbiologist colleagues as the primary authority on infection control nursing.

3. ROLE AND COMPOSITION OF INFECTION CONTROL TEAMS

3.1 Expert guidance originally published in 1988 and updated in 1995 (HSG(95)10) recommends that all acute hospital Trusts employ at least one infection control nurse to co-ordinate day-to-date activities.(1) Currently, the majority of hospital Trusts in the UK employ one or two qualified ICNs. The same guidance recommends that a medical microbiologist take on the role of infection control doctor (ICD) for a number of sessions per week dependent on the size of the Trust and volume of activity.

3.2 Overall responsibility for ensuring that adequate and appropriate arrangements are in place for the detection, prevention, surveillance and control of infection lies with the Chief Executive of Trusts and with the Consultant for Communicable Disease Control (CCDC) for the health authority (HSG(93)56). Such arrangements should be explicitly required as part of the quality contracts agreed between purchasers and their providers of all patient care.(2) Unfortunately such contractual arrangements do not routinely exist. A recent small questionnaire survey of the ICNs in the Trent region revealed that the majority of infection control teams, both in the hospital and community do not have formal contracting arrangements with their purchasers. (May DA and Calrow EA unpublished work)

3.3 Changes and developments in health care organisation and delivery have established the need for a dedicated "community" infection control nurse (CICN) role, as community trusts are required to have in place infection control arrangements in line with HSG(95)10. Many Consultant for Communicable Disease Control (CCDC) positions are supported by ICNs. The evolution of the role has however been fragmented with the provision of posts being inconsistent across the country. The problems associated with the control and management of multi-resistant organisms in the community setting make it imperative that community infection control service requirements are examined and adequate provisions are made to provide an effective service.

3.4 The vast majority of ICTs in acute hospital Trusts have no budgets whatsoever. Historically the infection control service is classed as a service which has been provided as part of pathology services but has often been centrally funded. There are few Trusts where the service is negotiated separately from microbiology and with independent funding. Many ICNs still do not have computer facilities to enable them to electronically collect, store and retrieve data and few ICTs have dedicated secretarial staff.

3.5 Only through the formalisation of contractual arrangements *which includes provision of adequate resources and a budget* will ICTs be able to develop the level of services necessary to cope with the increasing demands placed on them by the rise in antimicrobial resistance.

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4. METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

4.1 *Staphylococcus aureus* is a gram positive bacterium which can colonise the skin of human beings without causing any symptoms. It is characteristically found in warm, moist areas such as the nose, axillae and perineum and also readily colonises breaks in the skin such as surgical wounds, pressure sores (bed sores) and chronic skin lesions such as eczema. Outside of hospitals, 10–30 per cent of healthy adults are nasal carriers. There is a higher nasal carriage rate (in staff) in hospitals of between 20 and 60 per cent. (3)

4.2 Both the resistant and sensitive strains of *S. aureus* cause a wide spectrum of illnesses ranging from trivial skin infections to life threatening conditions such as bacteraemia, endocarditis and pneumonia.

4.3 The resistant strain of the organism—known as methicillin resistant staphylococcus aureus (MRSA) colonises the skin in exactly the same way, but certain risk factors increase the likelihood of acquiring the resistant, and subsequently more difficult to treat, variety. These risk factors include: increased age, admission to intensive care (ITU), previous hospitalisation, invasive procedures, recent antibiotics and congenital abnormalities.

4.4 Colonisation may be difficult to eradicate especially in the elderly or those requiring continuing care especially when colonisation occurs in long-term devices, e.g., urinary catheters, PEG (percutaneous endoscopic gastrostomy) tubes and chronic wounds such as pressure sores and leg ulcers. Those with chronic exfoliating skin conditions, e.g., eczema or dermatitis are also at increased risk of chronic colonisation, and this category of risk covers both patients and staff. Even with treatment, eradication of carriage is often temporary and all ICNS will know patients who are regularly re-colonised at various sites for weeks or months on end.

4.5 There is a wealth of data now available globally on the clinical importance of MRSA, with some data suggesting that MRSA may be associated with a higher mortality than methicillin sensitive *S. aureus* (4).

4.6 Treatment of severe infections with MRSA is more difficult because of increased antibiotic resistance. Treatment of choice is vancomycin or teicoplanin. Very recent reports provide evidence of emerging vancomycin resistance. (5)

4.7 Recent data indicates the importance of MRSA as a nosocomial (hospital-acquired) pathogen. The second national prevalence survey (6) showed colonisation with MRSA to be the highest relative risk factor with MRSA causing approximately 15 per cent of *S. aureus* surgical wound infections. Data collected by the Public Health Laboratory Service (PHLS) bacteraemia reporting system reflects an increasing incidence of MRSA infections, using bacteraemia as a marker of significant infection. Reported MRSA bacteraemias remained static at 1.8 per cent between 1989–1991; increased to 8.1 per cent. between 1992–1994 and 13.5 per cent in the first six months of 1995. (7)

4.8 MRSA from a hospital perspective

“It is difficult to justify the costs incurred from an intervention where the successful outcome measure is an event not occurring.”(8)

4.9 This statement is widely and frequently repeated by infection control practitioners and goes some way towards explaining the frustrations frequently experienced by infection control teams during their attempts to justify requests for increased resources. The cost of controlling MRSA can be broken down thus:

- direct patient care costs;
- management costs;
- intangible costs;

There have also been a number of studies which have analysed outbreak costs.

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4.10 *Direct patient care costs*

These include:

- “hotel” costs of extended length of stay;
- increased diagnostic procedures including screening for carriage;
- increased use of personal protective equipment;
- additional environmental cleaning costs;
- treatment costs:
 - antibiotics;
 - antiseptics;
- isolation procedure costs;
- use of single rooms/isolation units;
- disinfectants;
- antiseptic soaps/alcohol hand rubs;
- increased morbidity and mortality of MRSA infection;

4.11 *Management costs*

These include:

- temporary bed/ward/theatre closures;
- staff re-deployment;
- disruption of routine activity;
- costs attributed to staff colonisation/infection:
 - sick pay; redeployment; treatment;
- increased occurrence of litigation due to raised public awareness;
- delays in transfer to residential care as a result of:
- inadequate resources; lack of knowledge; insurance-related issues
- adverse publicity leading to damaged reputation and subsequent loss of referrals/contracts.

4.12 *Intangible costs*

These include:

- loss of earnings
- pain, anxiety, depression
- psychological effects of isolation/feeling “dirty”
- reduced quality of life
- additional support and/or treatment after discharge

There have been a number of significant studies analysing the costs of controlling outbreaks of MRSA. It is, however, difficult to compare these costs with those of an uncontrolled outbreak where, as a result, colonisation may become endemic with resultant long-term management difficulties. Costs have varied:

- £12,965 for London outbreak in ITU involving 36 patients.(9)
- over £400,000 for Kettering outbreak involving 400 patients.(10)
- over £700,000 for outbreak in Madrid involving 900 patients.(11)

4.13 *Infection Control Measures*

There are a number of standard infection control measures which are widely recognised by infection control teams as being essential in the management and control of MRSA *as well as other antibiotic resistant organisms*. Unfortunately there is often a perception amongst senior clinical medical staff and Trust managers that some of these measures are more disruptive than effective and this does not make comprehensive management and control any easier. These problems tend to arise as a result of increasing pressures on hospitals to admit and transfer patients rapidly—especially during the winter months of increased emergency activity—and the need to wait 48–72 hours for screening results to identify the presence (or absence) of MRSA upon which subsequent patient management decisions will be based.

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4.14 *Communication*

Early laboratory identification and subsequent communication between infection control teams and all carers is of vital importance. Communication between carers, especially across care boundaries is often inconsistent as well as time consuming for poorly resourced ward staff and infection control teams.

4.15 *Isolation*

As MRSA is a skin-borne organism which can be transmitted in skin scales and household dust, it is standard practice to nurse affected patients in single rooms with the door shut to minimise the risk of environmental spread and subsequent cross-infection. Many older hospitals with open "Nightingale" wards have very few single rooms. These may also be needed by other patients such as the dying, making allocation a difficult choice. However, even in modern hospitals well equipped with single rooms there are problems. Many high dependency units do not have adequate isolation rooms to facilitate management of affected patients in what are high risk clinical environments. Some Trusts insist on carpets in side rooms—making the hospital environment more akin to a hotel, and more difficult to keep dust free—and in other Trusts the size of the MRSA problem is constantly greater than the number of single rooms available. There has also been a steady reduction in the number of isolation units in recent years possibly as a result of the need to optimise the use of resources to maximise income. Unfortunately many isolation units were closed in the late 1980s and early 1990s prior to the emergence of the epidemic strains of MRSA which are currently spreading more rapidly.

4.16 Where inadequate isolation facilities are available, affected patients can be "cohort-nursed" in bays or wards. This requires designated staff to care for affected patients thus separating patients and nurses into teams. Unfortunately cohort nursing is becoming increasingly difficult in view of the widespread reductions in permanently employed staff, significant alterations to the nursing skill mix and an increased reliance on agency staff who may well move from ward to ward and from hospital to hospital with little knowledge of local infection control policies and procedures.

4.17 *Handwashing*

Adequate and appropriate handwashing is well recognised as the single most important measure in infection control. Caring for patients with resistant organisms requires the use of more expensive antiseptic soaps and hand-rubs. These, in turn can lead to increased problems with skin conditions in nursing staff especially when cheaper products are used.

4.18 *Personal protective equipment*

There are significant additional costs incurred in providing disposable plastic aprons and latex gloves for all episodes of direct patient contact. These measures are essential to reduce transient carriage of micro-organisms on uniforms or hands of staff from one patient to another.

4.19 *Environment and equipment cleaning*

As MRSA survives for long periods of time (6-8 weeks) in dust particles, regular and thorough environmental cleaning is of particular importance. In some circumstances it is necessary to change bed and window curtains as well as carrying out thorough damp dusting and cleaning of all surfaces. Miscellaneous equipment e.g., mattresses, oscillating fans, and complex therapeutic bed systems used for pressure sore management etc., are often overlooked in cleaning schedules and have been implicated in outbreaks of infection (12). The introduction of competitive tendering has stretched some hotel service departments resources to such an extent that "terminal cleaning" following discharge of patients in isolation is reduced or, at best delayed thus impacting on patient throughput.

4.20 *Ward closure*

In the current economic climate within the NHS, it is becoming increasingly difficult for infection control teams to recommend what is often the most effective means of control—ward closure. Ward closure is not undertaken lightly and usually only as a result of an outbreak committee decision when other control measures have failed, or when the affected clinical area is considered to be high risk e.g., high dependency, cardio-thoracic and neonatal units.

4.21 However, the high risk to patients in such environments has to be off-set by the need to continue activity in an acute regional or national referral centre where no alternative facilities are available nearby.

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4.22 In services such as selective surgery, the risks of transmission may outweigh the benefits of admission thus making the decision to close wards an easier one. However, this is again off-set by the pressures of the waiting list initiative and Patient's Charter standards.

4.23 *Screening for the presence of MRSA*

There are differing expert opinions on the value of screening to detect the presence of MRSA colonisation.⁽¹³⁾⁽¹⁴⁾ However, the expert opinion of the combined working party (awaiting publication) is to recommend screening and it has clearly laid down recommendations for both patient and staff screening.

4.24 The increased incidence of MRSA together with a rapid increase in patient movement between acute hospitals and, indeed between wards in the same hospital, has lead to a significant rise in the frequency of routine screening of patients both on admission to, and discharge from clinical areas. Frequency and extent of screening usually depends on a risk assessment of the clinical area and varies from screening *all* admissions into regional referral centres to screening previous known cases/frequent re-admissions/transfers from affected nursing homes/transfers from abroad on admission to low risk areas such as medicine and health care of the elderly.

4.25 Screening usually involves taking bacteriological samples (swabs) from "carrier" sites namely the nose, axillae and perineum together with swabs from breaks in the skin such as surgical wounds, pressure sores, invasive devices, etc. Screening is usually carried out on known positive patients at weekly intervals. Three negative screens are required before infection control measures are discontinued, and as previously mentioned, re-colonisation frequently occur if invasive devices or skin breaks persist. Thus even transient carriage requires four separate sets of screens and can result in isolation for a minimum period of two weeks.

4.26 *Treatment for MRSA*

The eradication of carriage of MRSA is not always successful especially in chronic lesions such as leg ulcers and pressure sores. High and low level resistance to Mupirocin (the first line and most effective treatment for nasal carriage) is being increasingly reported, and topical antiseptics, usually used as body washes are not always effective. Also they may have a drying effect on skin especially in the elderly.

4.27 A usual course of topical treatment is five days. This requires regular monitoring to ensure that treatment does not exceed recommendations. Courses may require repeating if carriage is not eradicated with resultant increased costs.

4.25 Throat carriage, when identified, is often difficult to eradicate and may require systematic antibiotic treatment which has unpleasant side effects for the patient.

4.29 The treatment of colonised or infected surgical wounds, pressure sores and leg ulcers is often difficult and costly. Antiseptic cleansers may be required, together with specialist wound dressings containing chlorhexidine or povidone iodine. Systematic antibiotics may also be required for significant wound infections.

4.30 Systematic antibiotic treatment of significant infections is extremely costly, usually requiring intravenous antibiotics which often require frequent monitoring of blood levels. Most intravenous antibiotics have significant and unpleasant side effects.

4.31 A positive screen result indicating the presence of MRSA takes 48–72 hours to confirm. This can have significant implications for patient transfer especially into nursing homes or health care of the elderly beds and for bed management during emergency take days especially during winter months.

4.32 The recent development of a more rapid (and accurate) diagnostic screening method using molecular techniques to detect the *mecA* gene will significantly reduce this delay to one working day. However, current costs of £25 per screen may prove prohibitive, although the service will undoubtedly improve efficiency in patient management.

4.33 The significant increase in occurrence of MRSA and consequently in screening requests, has had a major impact on microbiology laboratories' ability to cope with the increased demands during a period of "down-sizing" and financial constraint. An increase in diagnostic microbiology will obviously result in a higher cost to Trusts for the provision of the service.

4.34 *Colonised staff*

There is currently no expert consensus on exactly when hospital staff should be screened for carriage of MRSA. As the problem of MRSA becomes endemic in more and more hospitals there is likely to be an increase in colonised staff, although most colonisation is usually transient in the absence of skin breaks.

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4.35 There have been unsubstantiated reports, however, of staff becoming chronically colonised with MRSA in eczematous skin lesions and in the ear. On occasions staff have been re-deployed to lower risk areas. There is also anecdotal evidence of staff losing their jobs as a result of MRSA carriage and also of staff being turned down for employment as a result of pre-employment screening identifying carriage. As MRSA is not classified as an industrial disease this does leave affected staff unprotected and unable to claim recompense.

4.36 Education

One of the primary responsibilities of ICNs is the training and education of all grades of healthcare staff in the multidisciplinary NHS. This includes nurses; professions allied to medicine; ancillary staff; technical and clinical support staff and junior medical staff.

This education may take the form of formal and/or informal lectures, induction programmes and the provision of written policies and procedures for staff to follow.

4.37 Education and training is essential but also extremely time consuming, for both ICNs and the staff requiring training. Staffing levels across the health service are often at a level where staff cannot be released for non-essential training. This is especially true in areas like domestic and portering services where there are frequent vacancies. Unfortunately such staff are most in need of training due to their lack of basic infection control knowledge. Such staff groups frequently over-react to situations such as providing a service to patients in isolation. This over-reaction is often compounded by inaccurate and inflammatory media attention, and leads to staff going to various extremes such as wearing unnecessary protective clothing whilst accompanying a patient to x-ray, or refusing to clean an isolation room for fear of taking MRSA home.

4.38 The lack of adequate resources to provide sufficient infection control nurses often means that comprehensive Trust-wide training cannot be undertaken even in a methodical and planned training programme due to the reactive nature of the service and the pressures placed upon it by outbreaks of infection, including MRSA.

4.39 Surveillance

There is currently no standardised national data collection system in operation in the UK which allows for comparison over time and between centres.

However, substantial data is collected by the Public Health Laboratory Service although the system is voluntary. A recent meeting, convened by the PHLS at Colindale, chaired by Dr J Weinberg and attended by a medical officer from the DOH as well as representatives from all expert parties, identified the urgent need for a minimum data set to be collected from all NHS hospitals in order to determine the extent of the current problem. The joint working party on MRSA also makes explicit recommendations for the epidemiological assessment of MRSA (4).

4.40 Currently, most ICTs collect data on MRSA as part of alert organism surveillance. The nature and extent of the data will be determined locally, usually as part of contractual arrangements. It may, however, only be reported if an outbreak is deemed to have occurred, not routinely.

4.41 ICTs also carry out targeted and/or selective surveillance of organisms other than MRSA. This may take the form of surveillance of surgical wound infections, ventilator-associated pneumonias, bacteraemias etc. The DOH funded Nosocomial Infection National Surveillance Scheme (NINSS) co-ordinated by the PHLS offers the opportunity for Trusts to participate (voluntarily) in a nationally co-ordinated selective surveillance scheme. This project has real potential and many ICTs have signed up to the first two modules currently under development. It must be borne in mind, however, that surveillance *per se* is very labour intensive. A significant study carried out by Glenister *et al* (15) showed that the most effective type of surveillance—laboratory based ward liaison surveillance—required from 3–6.8 hrs./100 beds per week to perform effectively.

4.42 These are also considerable problems involved in trying to identify the extent of community reservoirs of MRSA, especially in nursing homes. Early discharge means that the problem is often identified by GPs and the lack of both post-discharge surveillance and community ICNs means that, with the exception of localised studies, such as that carried out in Kettering (16), there is no comprehensive data available which reveals the extent of the problem being imported into our hospitals as community acquired infections.

4.43 MRSA—a community perspective

The number of patients affected with MRSA appears to be increasing. (17)

4.44 Hospitals have implemented MRSA control protocols ranging from minimal intervention to a “search and destroy” policy. In the community however, infection control varies throughout the country and in some areas this may result in the community reservoir of MRSA expanding.

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4.45 Evidence suggests that we need to look more closely at the extent to which nosocomial pathogens are transmitted in the community. Although the emphasis is now placed on care pathways or “seamless” care across providers, antibiotic-resistant organisms continue to be categorised as acquired either in the community or in hospital. (18)

4.46 The spread of MRSA in nursing and residential homes and reintroduction of MRSA into a hospital by patients admitted from nursing homes has been reported. (16)(10) If MRSA is to be effectively controlled in all care settings the close collaborative working between CsCDC and consultant microbiologists is essential.

4.47 There is much anxiety about the spread and significance of MRSA in community settings such as nursing and residential homes. In some parts of the country, patients colonised with MRSA are refused admission to nursing homes when discharged from hospital. This has major repercussions on affected patients and hospitals.

4.48 The number of frail elderly people in residential, nursing home care is increasing, and they constitute an important population to be considered. About 170,000 nursing home beds were operational in the UK in 1993 compared with some 60,000 in long-term geriatric and psychiatric health service units. (19) In addition there are many more residential home beds; that may be an important consideration because of the lack of professional nursing skills and increasing dependency. Infection and infection control is likely to be a major issue, for example, colonisation with MRSA has been shown to be a predictor of subsequent infection in nursing home residents. (20)

4.49 Over a 21 month period an outbreak of MRSA infection occurred in North Northamptonshire. The outbreak was caused by a novel phage type (EMRSA—16) and affected 400 patients. It was centred on three hospitals but spread was also detected in the community, particularly among clients of nursing and residential homes. Three hundred and fifty residents in 15 care homes were screened for MRSA. Cross infection of MRSA was demonstrated in 14 patients in six different homes. A key aspect of the overall containment of the outbreak was the implementation of infection control measures in the community, together with treatment and screening of known positive patients following their discharge from hospital. (16)

4.50 An MRSA prevalence study is at present being undertaken in some nursing homes in this part of Northamptonshire. Homes were chosen at random and then gave permission to be part of the study. Screening is being supported by infection control advice and information on MRSA.

4.51 An anonymised point-prevalence survey of MRSA carriage was conducted amongst a stratified random sample of nursing home residents in Birmingham, UK during 1994. One hundred and ninety-one residents took part, 33 (17 per cent) were MRSA positive with only one of these having a clinical infection. Environmental samples were taken with 10 positive results from 87 samples. Phage typing revealed similarities with those circulating in the Birmingham hospitals. The findings of this study suggests that prevalence of MRSA in nursing homes in Birmingham was high (17 per cent) and that the strains may have originated in hospitals. (21)

4.52 Advice on MRSA in community settings was sent out in May 1996 to all nursing and residential homes from the Department of Health. (22)

4.53 Community numbers of MRSA may only be the tip of the iceberg because not all patients with MRSA are overtly clinically compromised. Community strains are identified usually because there is an obvious clinical infection brought to the attention of an alert general practitioner or district nurse. (23) Subacute or chronic low grade infections, catheter-related urinary sepsis or colonised-only patients probably go unnoticed. MRSA is on the increase and the true extent to which the community is affected is unknown.

4.54 Currently a two tier management approach to MRSA is common in which a patient's own home, residential and small group home settings are considered against the nursing home settings (where the host risks of acquiring MRSA are considered to be greater). Rather there is a need to assess each individual care establishment, to ensure adequate provision for handwashing, appropriate availability of protective clothing and a minimum basic level of staff hygiene knowledge and practice. This may have significant resource implications.

4.55 Placement by social service personnel of those persons colonised or infected with MRSA needs to be carefully considered to fulfil both the individuals' social and general care (including clinical care) needs.

4.56 The interface between community and the acute care sector must be seamless, with clear lines of communication, responsibility and support in place.

4.57 The availability of education and support for the care and management of individuals with MRSA remains essential for all staff and affected individuals in the community setting both within and outside the health service. This will help avoid inappropriate management of those colonised or infected with MRSA and also to avoid problems of bed blocking in the acute hospital setting. It must be remembered that a higher proportion of carers in the community setting are untrained staff. The turnover of such staff is also high. This has major implications for the workload of community ICNs whose remit is to provide education and training for all staff groups.

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4.58 The lack of comprehensive epidemiological information on MRSA may be detrimental to effective control policies. However, this information would be both very difficult and costly to collect.

4.59 *Hospital staff's perceptions of MRSA colonisation*

The following information comes from a small unpublished study of hospital staff's perceptions of being colonised by MRSA. (MacKenzie D unpublished work)

4.60 During outbreaks of MRSA at one acute hospital trust, staff were screened to ascertain if they had become carriers of MRSA. On one occasion, as many as 15 staff in an out-break involving 19 patients were found to be colonised. During these outbreaks, many of the colonised staff became distressed, expressing feelings of fear, anger, disgust and guilt; some cried. The following are some examples of how staff were affected by MRSA.

4.61 Some affected staff did not "sleep" with their husbands until they had undergone treatment and been cleared of MRSA carriage. Affected staff were shunned by their work colleagues and families, receiving no phone calls or communications during the time they were colonised by MRSA. One staff member did not see her brother, his wife or their children for three months until she had been pronounced MRSA negative for three consecutive weeks. There were not isolated instances as infection control nurses in other trusts had experienced similar issues from staff who were colonised.

4.62 The main feelings that staff exhibited were fear, guilt, conflict, and the feeling of being "dirty". Some of these emotions were also expressed by patients.

4.63 *Fear*

Fear and having a dread of passing MRSA on to friends and families were common concerns. The fear that they may continue to be MRSA positive for a long time was frequently expressed. Often, long term career prospects were referred to with the staff member feeling that he or she would become unemployable the longer they were MRSA positive.

4.64 In the shorter term, worry was voiced regarding being moved from their area of work, maybe to work in non patient care areas. This was a particular problem for staff members who became colonised more than once, or who had been suspended from work for weeks or months for treatment and eradication of MRSA.

4.65 *Guilt*

Guilt and blame were closely linked. Some staff blamed themselves for picking up and spreading MRSA. Staff who worked in areas which had several outbreaks of MRSA and who were found to be colonised on more than one occasion were particularly affected. These staff appeared to become more anxious each time they were found to be MRSA positive. Furthermore, guilt was felt at being suspended from work when they were not ill. This in turn led them to feeling that they were somehow letting their colleagues down.

Some staff blamed themselves for being the cause of outbreaks. When patients were very ill with MRSA infection, or if MRSA was implicated in the death of a patient, it was not uncommon for the staff to blame themselves for being the cause of the patient's illness or death.

4.66 *Conflict*

Current working party guidelines advised that staff be suspended from work for 24-48 hours to start mupirocin treatment. This in itself caused conflict. Non-affected staff generally deduced what was happening to their colleagues. Staff confidentiality was, therefore, breached.

4.67 Other contentious issues surrounded staff shortages where MRSA positive staff were asked to remain on duty, although they had been told by the occupational health staff that they should not be at work.

4.68 *Feeling dirty*

Not all staff felt dirty, but for those who did, the experience was profound. These staff talked of "crawling" with bugs, or saying they felt "like a leper". Their feelings of being dirty were also linked to fear that they may be accused by colleagues of lack of care for their patients. Even at home, staff carried out stringent infection control precautions. For example, houses were scrubbed with bleach; hand washing and bathing for some, became excessive.

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4.69 Staff support

In the study outlined here, staff were sensitive to MRSA colonisation and the majority of them would have given anything not to have gone through the experience. The majority of ICNs have become proficient in managing issues relating to MRSA because of the increasing problems they are facing with the organism and such staff are frequently sought out to counsel MRSA affected staff.

4.70 In the past few years, ICNs have had to adapt to the increase in workload generated by MRSA without additional resources. Staffing issues are bound to increase this workload even further.

5.1 Vancomycin-resistant enterococci (VRE)

Bacterial resistance is a major problem in the effective treatment of infection. The results of resistance are twofold—firstly, treatment failure and secondly increased costs (24) associated with increased length of stay in hospital, expensive antibiotics and infection control procedures to prevent spread.

5.2 There are 12 enterococci species, *Enterococcus faecalis* and *Enterococcus faecium* being the two primary species documented as causing varying infections. (25)(26)

5.3 Enterococci are essentially normal gut flora but have been identified as potentially pathogenic since the turn of the century. The enterococci are inherently resistant to many antibiotics, including all cephalosporins. Indeed, the increased prevalence of enterococcal infection may be related to the increase in cephalosporin use over the last 20 years. However, vancomycin resistance generally means that the organism may not be sensitive to any available antibiotic.

5.4 Vancomycin resistance in enterococci is often looked for by mobile genetic element which may be transferred to other more virulent bacteria, such as *S. aureus*, resulting in glycopeptide resistance in these organisms, namely a vancomycin-resistant MRSA.

5.5 The epidemiology of VRE is not well understood. Patients can become colonised or infected through environmental contact with the organism and high standards of cleaning are imperative. Patients with diarrhoea are more likely to shed bacteria into the environment (27). Colonisation of the gut with VRE does not, however, result in diarrhoea.

5.6 American guidelines (28) recommend that all patients with VRE be isolated. In the UK this is essentially impractical, given limited isolation facilities and their use for other infection control alert organisms.

5.7 Despite documented outbreaks, the pathogenic potential is controversial. (29) Mortality from VRE bacteraemia/septicaemia is high, yet remains so even with sensitive strains. The current problems are unique as there is no consensus on effective treatment.

5.5 To control further increased incidence the prudent use of vancomycin is imperative.

6.0 Aminoglycoside resistance

History

Since the 1960s reports of antibiotic resistant bacteria in hospitals have appeared with increasing frequency. (30) In the 1970s and 1980s the emergence of aminoglycoside resistance in nosocomial Enterobacteriaceae and *Pseudomonas* was seen. Some infection control teams have to use a marker such as gentamicin resistance in Gram negative bacilli to monitor the epidemiology of aminoglycoside resistance in hospital. However, it is recognised that “silent outbreaks” have occurred in many hospitals and only been identified when investigation of clusters of infection took place.

6.1 Vulnerable populations

To date, most of the problems of aminoglycoside resistance have been seen in patients nursed in intensive care and high dependency units e.g., renal units in both the adult and paediatric populations. (31)(32) The greatest problem has been recognised in large hospitals and teaching institutions. Patients received into the UK from countries such as Greece, France, southern Europe and the Middle East, where the problem of antibiotic resistance is endemic, are frequently colonised with these organisms and act as a reservoir of infection.

6.2 Principle reasons for aminoglycoside resistance

Excessive and inappropriate use of aminoglycosides has resulted in the emergence of multiple resistance. Use of topical aminoglycoside ointments and use of nonabsorbable aminoglycosides in enteral regimens for suppression of gut bacterial have also probably contributed.

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6.3 This excessive and inappropriate use may be due to:

- anxiety on the part of the clinician to use more potent antibiotics and the latest drugs because of resistance;
- increasingly critically ill and immunocompromised/immunosuppressed patients who are susceptible to a wide range of pathogens and opportunistic infections;
- over interpretation of colonisation e.g., *Pseudomonas* in ITU, increasing the use of unnecessary broad spectrum antibiotic treatment;
- lack of antibiotic prescribing policies and audit of use.

6.4 *Transmission*

Spread is principally via the exogenous route, either person-to-person or by environmental reservoirs.

6.5 Person-to-person spread by:

- inconsistent application to basic infection control measures by healthcare workers such as handwashing and the wearing of protective clothing such as gloves and aprons;
- increased patient colonisation (e.g., gastrointestinal) leading to reservoirs of infection. Colonised patients may be unidentified as microbiological admission screening (e.g., nose/throat swabs and stools) are frequently not taken;
- factors which increase person to person spread are overcrowding in units and reduced nurse/patient ratios;
- although staff gastrointestinal colonisation has been cited this has not been identified as the most likely route of spread. However hand colonisation is well documented and cited as a mode of spread; (33)(34)(35)

6.6 Environmental spread

- contaminated equipment such as ventilators, suction equipment, bedpan disposal equipment, urine measuring devices etc. which have been inadequately decontaminated have been identified as reservoirs.
- cleaning equipment such as mops, buckets, cloths and spray cleaners have been cited as contaminating the environment. There are currently no universal domestic cleaning standards laid down;
- food has been cited as a source especially in oncology units;
- although reservoirs of resistant Gram negative bacilli have been identified in contaminated water such as sinks and flower water, epidemiological evidence of spread has only been identified in high-risk immuno-suppressed patients. This is not felt to be a common source. (36)
- vectors such as flies and cockroaches are probably unimportant in the transmission of resistant bacteria in the UK.

6.7 *Control measures*

The control measures known to be effective are generally the same as for all antibiotic resistant organisms:

- increase frequency of handwashing before, during and after patient contact;
- increase environmental cleaning and monitor standards regularly;
- target microbiological surveillance of "at risk" patients. (37)
- reduce intra-hospital transfer of colonised patients. Inform receiving hospital or health care facility of colonised patients;
- assess the patients risk factors of spreading the organism and isolate the colonised/infected patient if necessary, e.g., in high risk specialties. Encourage good hygiene standards in the patient.
- use protective clothing such as gloves and aprons when nursing all patients but especially those colonised/infected with resistant bacteria;
- discontinue compromising factors such as naso-gastric tubes and urinary catheters as soon as possible. Rotate intravenous sites regularly and avoid femoral lines where possible. Change respiratory equipment regularly and use gloves for suction;
- equipment should be adequately decontaminated or sterilised as appropriate and an audit trail should be in place for process surveillance.
- all units should have antibiotic prescribing policies which have been agreed by the local consultant microbiologist and consultant clinician of the specialty;

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- increase education to all disciplines in health care, including patients;
- written information should be available to staff, visitors and patients.

7. Drug resistant tuberculosis

This evidence is concerned with tuberculosis transmitted via respiratory droplets, principally infectious pulmonary tuberculosis caused by *Mycobacterium tuberculosis*. Tuberculosis in other sites, i.e., extra-pulmonary tuberculosis, does not usually pose a risk to others.

7.1 Tuberculosis has been recognised for centuries, and has always been associated with poverty and disadvantaged groups (38)(39). In 1993, the World Health Organisation described tuberculosis as a global emergency (40) recognising the significant associated morbidity and mortality. An increase in the incidence of tuberculosis has also been reported in the UK, where notifications of tuberculosis rose by 17.2 per cent (41). The most dramatic increase has been seen in inner London (42).

7.2 Since the advent of antituberculosis treatment, resistance to these agents has been reported in a small number of patients. However, in 1991–92, outbreaks of tuberculosis, associated with multidrug resistant strains of *Mycobacterium tuberculosis* (MDR-TB) were recorded in healthcare facilities in New York and Florida where both patients and staff were infected, most of whom were HIV positive. A mortality rate of 70 per cent was recorded in those infected with MDR-TB (43). Two instances involving nosocomial transmission of tuberculosis on HIV units has also been reported in the UK. (44)(45)

7.3 Multidrug resistant tuberculosis, i.e., disease due to *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin with or without resistance to other anti-tuberculosis drugs can be either primary drug resistance: disease due to acquisition of infection with a drug resistant organism or acquired (secondary) drug resistance: disease which has become drug resistant during treatment, usually as a result of inadequate or incomplete treatment.

7.4 The principal groups in the UK where MDR-TB has been diagnosed are HIV positive patients, and those from sub-Saharan Africa and some Mediterranean countries, e.g., Portugal.

7.5 Key infection control issues

Maintaining a high index of suspicion for diagnosing tuberculosis, including those with MDR-TB, to ensure prompt identification and commencement of anti-tuberculosis therapy. The greatest infection control risk is from those patients not diagnosed. Mathur (46) demonstrated the scope of this problem.

7.6 *Mycobacterium tuberculosis* is a slow growing organism and it currently takes four to six weeks before drug sensitivities are known, and it can be confirmed whether adequate treatment is being administered or if a multidrug resistant strain has been isolated. New technologies are being developed to hasten this process.

7.7 Clinical tuberculosis disease can develop many years after a person was originally infected, usually when there is a deterioration in the immune system due to ageing, immunosuppression, etc. Potentially, it may be many years before the infection becomes apparent in some exposed persons, e.g., health care workers.

7.8 Patients that are immunocompromised, e.g., HIV positive persons are more likely to have an atypical presentation of tuberculosis, and there is a greater risk that the infection may not be immediately diagnosed in such patients, which increases the likelihood that the infection may be transmitted to others. HIV positive patients are at greatly increased risk of developing clinical disease if infected.

7.9 All healthcare workers should have had BCG vaccination or have their immunity to tuberculosis confirmed with a Heaf test. BCG vaccination has been shown to have an efficacy in protecting against tuberculosis of 70–80 per cent when given to British school children, with protection lasting at least 15 years (47). However, there is no current recommendation as to whether health care workers exposed to patients with infectious tuberculosis should have enhanced health surveillance. It is recommended that healthcare workers who are immunocompromised should not care for such patients, both because of their increased risk of becoming infected, and the potential risk that they could transmit the infection to other patients.

7.10 It should be remembered that the key to prevention of tuberculosis transmission in hospitals is prompt diagnosis of infected patients, and that outbreaks have occurred due to failure to implement infection control precautions.

7.11 The control of MDRTB in the community includes not only the management of individual patients and their contacts as they present but also requires current assessment and development of existing and recommended preventive TB services for the high risk groups such as homeless persons and immigrant populations.

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7.12 Key recommendations

There is a need to educate all health care workers about recognition and treatment of tuberculosis, and the importance of communication of all those involved in patient care, including clear interface between acute units and the primary health care teams. Advice should always be sought by clinicians about treatment for tuberculosis from those have expertise in this area, i.e., chest physicians, TB nurses, medical microbiologist, HIV physicians, etc. Clear guidance is required for deciding when a patient is no longer infectious and the chest physicians should be consulted about this.

7.13 Compliance to treatment is essential to prevent development of new drug resistant strains, and all hospitalised patients should have directly observed therapy.

7.14 Adequate facilities for nursing patients, e.g., negative pressure rooms are required. However, some MDR-TB patients are hospitalised long term, and therefore these facilities can become blocked.

7.15 Consideration must be given to the effect on the patient of being isolated in a single room long term. Tuberculosis remains a stigmatising illness, and there are anecdotal reports that persons co-infected with HIV and MDR-TB have been ostracised by their own community.

7.16 Consideration needs to be given to the problems encountered in maintaining an infectious individual in the domestic setting, namely:

- restricting patient movement to their home environment for a given period;
- restricting visitors from having contact with the patient;
- obtaining compliance with treatment;
- decontamination of equipment taken into the home;
- disposal of clinical waste (sputum pots, tissues, etc.);
- the use of protective clothing (who wears the mask?).

7.17 Consideration should be given to the need for using an “incident team” (a small trained and experienced team) to manage all MDRTB cases.

7.18 The roles and responsibilities of key individuals will need to be agreed and established, e.g., Communicable Disease Team, TB health visitors, district nurses, etc.

7.19 Comprehensive guidance has been published by the Department of Health (48) and British Thoracic Society (49)(50)(51) about the management of patients with tuberculosis. Additionally, the Department of Health will shortly be publishing guidance of the management of immunocompromised patients with tuberculosis and those with MDR-TB.

8. In conclusion

Having drawn together all the evidence, it is the considered opinion of the authors that there are a number of key issues which are of importance in considering future activity to control the spread of infection resulting from the rise in antimicrobial resistance. These are:

cost implications

- both of prevention and control.

manpower implications

- healthcare workers
- infection control nurses
- laboratory technicians

bed activity implications

- within Trusts
- within residential care homes
- between providers

8.1 In addition, there has been a significant increase in publicity surrounding the issue of antimicrobial resistance in recent years. This has lead to heightened awareness—and increasing concern—by healthcare workers and the general public of risks relating to the acquisition of resistant organisms both in hospital and the community at large.

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9. Recommendations

It is the considered opinion of the authors of this report that there are a number of recommendations which can be applied to all the antibiotic resistant micro-organisms identified within this report:

1. Improved epidemiological surveillance, preferably standardised across the country. This is of particular importance with MRSA, where a minimum data set should be identified possibly using clinical infectious as the numerator data.
2. Increased resourcing for infection control teams to enable comprehensive surveillance and education to be undertaken.
3. Standardisation of contracting requirements across all providers of care.
4. Standardisation of management and screening of MRSA at local/national level.
5. Public information campaign.
6. More emphasis should be placed on compliance with (and monitoring of) basic infection control measures, preferably through the contracting process.

REFERENCES

1. Shanson D C (1989) *Microbiology in clinical practice* 2nd edition Wright.
2. BSAC/HIS/ICNA *Draft revised guidelines on the control of MRSA in hospitals* (Chairman, Professor G A J Ayliffe)—out for consultation.
3. Hiramatsu K and others (1997) Methicillin-resistant *S. aureus* clinical strain with reduced vancomycin susceptibility *Journal of Antimicrobial Chemotherapy* 40: 135-136.
4. Emmerson A M and others (1996). The 2nd national prevalence survey of infection in hospitals—overview of the results. *Journal of Hospital Infection* 32: 175-190.
5. Johnson A P and others (1997) Epidemiology of antibiotic resistance: blood and cerebro-spinal fluid *Journal of Medical Microbiology* 6: 442-445.
6. Department of Health (1995) *Hospital Infection Control—HSG(95) 10* HMSO.
7. Department of Health (1993) *Public health: responsibilities of the NHS and the role of others—HSG(93)56* HMSO.
8. Casewell M W (1995) Cost-effectiveness of topical antibiotics and antiseptics for the control of MRSA In: Bruin-Buisson C and others (Editors) *Methicillin resistant Staphylococci* Paris Medicine-Sciences 141-148.
9. Mehtar S and others (1989) Expenses occurred during a five-week epidemic of methicillin resistant *S. aureus* *Journal of Hospital Infection* 13: 199-220.
10. Cox R A and others (1995) Major outbreak of methicillin-resistant *S. aureus* caused by a new phage type (EMRSA-16) *Journal of Hospital Infection* 29: 87-106.
11. Coello R and others (1994). Prospective study of Infection, colonisation and carriage of methicillin resistant *S. aureus* affecting 900 patients *European Journal of Clinical Microbiology and Infectious Diseases* 13: 74-81.
12. Loomes S (1988). Is it safe to lie down in hospital? *Nursing Times* 84: 49 63-65.
13. Cookson B (1997). Is it time to stop searching for MRSA? *British Medical Journal* 314: 1 March 664-665.
14. Teare E L, Barret S P (1997). Stop the ritual of tracing colonised people *British Medical Journal* 314 1 March 665-666.
15. Glenister H M and others (1993). Introduction of laboratory-based ward liaison surveillance of hospital infection into six district general hospitals *Journal of Hospital Infection* 25: 161-172.
16. Cox R A and others (1995). Epidemic methicillin resistant *S. aureus*: controlling the spread outside hospital *Journal of Hospital Infection* 29: 107-119.
17. Humphreys H, Duckworth G (1997). Methicillin-resistant *S. aureus* (MRSA)—a re-appraisal of control measures in the light of changing circumstances *Journal of Hospital Infection* 36: 167-170.
18. Decker M D, Schaffner W (1992). The relationship between the hospital and community. *Hospital Infections* Boston Little & Brown 221-230.

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[Continued

19. Laing R (1994). Care of the elderly and physically disabled. *Laing's review of private healthcare* Laing and Buisson 183.
20. Muder R R and others (1991). Methicillin-resistant staphylococcal colonisation and infection in a long-term care facility. *Annals of Internal Medicine* 114: 107.
21. Fraise A P and others (1997). Methicillin-resistant *S. aureus* in nursing homes in a major UK city: an anonymised point prevalence survey. *Epidemiology and Infection* 118: 1-5.
22. Department of Health (1996). *Methicillin-resistant S. aureus in community settings*—PL CMO (96)3 HMSO.
23. Hollyoak V (1996). Guidelines on the control of methicillin-resistant *S. aureus* in the community (letter) *Journal of Hospital Infections* 32: 81-82.
24. Levy S B and others (1987). Antibiotic use and antibiotic resistance worldwide. *Review of Infectious Diseases* suppl. 3: s231-s316.
25. Lewis M C and Zevros M J (1990). Clinical manifestations of enterococcal infection. *European Journal of Microbiology and Infectious Diseases* 9: 2: 111-117.
26. Gray J and others (1994). Enterococcal bacteraemia—a prospective study of 125 episodes. *Journal of Hospital Infection* 27: 179-186.
27. Boyce J M and others (1994). Outbreak of multi-drug resistant *Enterococcus faecium* with transferable Van B class vancomycin resistance. *Journal of Clinical Microbiology* 32: 1148-1153.
28. Hospital Infection Control Practices Advisory Committee (HICPAC) (1995). Recommendations for preventing the spread of vancomycin resistance: Recommendations of HICPAC *American Journal of Infection Control* 23: 87-94.
29. Quale J and others (1996). Experience with a hospital-wide outbreak of vancomycin resistant enterococci. *American Journal of Infection Control* 24: 372-279.
30. Casewell M W and Phillips L (1997). Hands as a route of transmission for *Klebsiella* species. *British Medical Journal* 2: 1315-1317.
31. Gould D J and Ream E (1993). Assessing nurses hand decontamination performance *Nursing Times* 89: 23: 47-50.
32. Larson E and Killien M (1992). Factors influencing handwashing behaviour of patient care personnel. *American Journal of Infection Control* 10: 93-99.
33. Goldmann D A and Huskins W C (1997). Control of nosocomial antimicrobial resistant bacteria: a strategic priority for hospital worldwide. *Clinical Infectious Diseases* 24 (suppl 1): s139-145.
34. Brun-Buisson and others (1989). Intestinal decontamination for control of nosocomial multi-resistant Gram-negative bacilli. Study of an outbreak in an intensive care unit. *Annals of Internal Medicine* 110: 873.
35. Hobson R P and others (1996). An outbreak of multiply resistant *Klebsiella pneumoniae* in the Grampian region of Scotland. *Journal of Hospital Infection* 33: 249-262.
36. Goovadia Y M and others (1992). Multi-resistant *Klebsiella pneumoniae* in a neonatal nursery; the importance of maintenance of infection control policies and procedures in the prevention of outbreaks. *Journal of Hospital Infection* 22: 197-205.
37. Bryce E A and Smith J A (1995). Focused microbiological surveillance and Gram-negative Beta-lactamase-mediated resistance in an intensive care unit. *Infection Control and Epidemiology* 16: 331-334.
38. Spence D P S and others (1993). Tuberculosis and poverty. *British Medical Journal* 307: 759-761.
39. McKeown T (1976) *The modern rise of the population* London Edward Arnold.
40. Godlee F (1993). Tuberculosis—a global emergency. *British Medical Journal* 306: 1147.
41. Hayward A C, Watson J M (1995). Tuberculosis in England and Wales 1982-1993: notifications exceeded predictions. *Communicable Disease Report CDR Review* 5: R29-33.
42. Coker R and Miller B (1997). HIV associated tuberculosis *British Medical Journal* 314: 1847.
43. Raviglione M C and others (1995) Global epidemiology of tuberculosis *Journal American Medical Association* 273: 220-226.
44. Scott G M and Holton J (1994). Transmission of tuberculosis by patients with HIV infection *British Medical Journal* 309: 1515.

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[Continued

45. Communicable Disease Report (CDR) weekly (1995). Outbreak of hospital-acquired multidrug resistant tuberculosis *CDR Weekly* 5: 161.
46. Mathur P and others (1994). Delayed diagnosis of pulmonary tuberculosis in city hospitals. *Archives of Internal Medicine* 154: 306-310.
47. Department of Health (1996). *Immunisation against Infectious Diseases* HMSO.
48. Interdepartmental Working Group on Tuberculosis (1996). *The prevention and control of tuberculosis in the United Kingdom: Recommendations for the prevention and control of Tuberculosis at local level* Department of Health.
49. Joint Tuberculosis Committee of the British Thoracic Society (1994). Control and prevention of tuberculosis in the United Kingdom: Code of Practice *Thorax* 49: 1193-1200.
50. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society (1992). Guidelines on the management of tuberculosis and HIV infection in the United Kingdom *British Medical Journal* 304: 1231-1233.
51. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society (1990). Chemotherapy and management of tuberculosis in the United Kingdom: recommendations of the Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 45: 403-408.

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Examination of witnesses

MISS SUSAN MACQUEEN, Clinical Nurse Specialist in Infection Control, Hospital for Sick Children, Great Ormond Street, Chairman of the Infection Control Nurses Association, MRS DEE MAY, Senior Nurse in Infection Control, Queen's Medical Centre, Nottingham, former Chairman of the Infection Control Nurses Association, and MRS JOAN LEWIS, Community Infection Control Adviser, Worcester Health Authority, from the Infection Control Nurses Association, were called in and examined.

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Chairman

200. May I ask you first of all to introduce yourselves and describe briefly the functions of the infection control nurse.

(*Mrs May*) My name is Mrs Dee May. I am the senior nurse for infection control at the Queen's Medical Centre in Nottingham. I have been an infection control nurse for ten years and until last month I was the chairman of the Infection Control Nurses Association for the preceding three years.

(*Miss Macqueen*) My Lord Chairman, my name is Susan Macqueen. I have been an infection control nurse for 18 years now working in the United Kingdom and abroad. I am at present at Great Ormond Street Children's Hospital, a senior nurse in infection control there, and I am taking over from Dee May as chairman of the Infection Control Nurses Association.

(*Mrs Lewis*) My Lord Chairman, I am Joan Lewis. I am a community infection control nurse. Prior to that I was a hospital infection control nurse and have spent 11 years in infection control. Prior to that I was a TB health visitor so multidrug resistant TB is something that is also of great interest to me. I work for a consultant in communicable disease control—CCDC—in the public health department, but many of my colleagues in community infection control actually work for community trusts, which are community hospitals, district nursing, that type of service.

201. What are the appropriate **staffing and training levels** for infection control nursing in a district general hospital for both specialist infection control staff and general nursing staff? Are these levels ever achieved in practice?

(*Miss Macqueen*) The Americans have shown that hospital acquired infection can be reduced by about 30 per cent if there is a ratio of one infection control nurse to 250 beds. However, they do carry out much more surveillance than we do in this country and they have less of a profile clinically at ward level or in the community. In the United Kingdom the average infection control nurse looks after 700 acute beds and a recent survey by the Public Health Laboratory Service identified a range of 125 to 1,600 beds per infection control nurse in this country, and that was a median of 460 based on 19 district general hospitals. This ratio in this country is really providing us with a reactive service rather than a proactive service because we would certainly like to do more significant surveillance. The minimum recommended training requirements for infection control nurses is a post basic diploma level course in infection control and previous management experience at sister or charge nurse level. Most NHS trusts comply to this. However, some private hospitals do not. There are teams of infection control nurses in some trusts and in the community. Some have junior infection control nurses who have not undertaken this training yet, but start the job for about a year and then do the course afterwards. As to general staffing, my Lord Chairman, I do not feel that I can talk about general staffing in hospital because for isolation units there is not a standard as to how many general nurses work in an isolation unit. There is no doubt that levels have been badly hit by a freezing of

vacancies and by the impact of Project 2000, the training course for nurses now. Student nurses are now supernumerary whereas before they were being used to care for the patients, and there are also significant recruiting problems now. The Royal College of Nursing and other unions have demonstrated that there are now about 50,000 nurses less than in 1989 so we are 50,000 fewer. There is no doubt now that there is a higher ratio of untrained staff to trained staff both in the community and in hospital. The intangible costs of an infection control team are very difficult to put in money terms, but there should be at least one infection control nurse and one infection control doctor. The releasing, when it comes to teaching, of clinical staff for training is very difficult and increasingly we are getting fewer people attending educational sessions. This includes people like porters and domestic staff, as an example, not just the professional staff. Then information technology costs: not all infection control nurses have access to IT. There is no doubt that this helps us in our work. None of us, or very, very few, have access to a full time secretary or a data clerk. Increased environmental cleaning levels: when you are going visiting, my Lord Chairman, you will certainly see a difference in the hygiene aspect and environmental cleaning in hospital, certainly from overcrowding, certainly from increased use of equipment and, if you look at curtain rails and under the beds, I think, you will certainly see layers of dust. This plays an important role in cross-infection.

Baroness Platt of Writtle

202. My Lord Chairman, perhaps I may just follow up the last point. I noticed in your paragraph 6.6 and paragraph 6.7 that there are no **domestic cleaning standards**?

(*Miss Macqueen*) No.

203. I can imagine that with a turnover of cleaners in hospitals it must be very difficult to keep standards up?

(*Miss Macqueen*) Yes, it is. There was a time when the domestic staff were part of the team under the auspices of the ward sister. That no longer occurs.

204. No.

(*Miss Macqueen*) Although people try to have a team approach so that people feel proud of their jobs, because some of these are very mundane jobs, they are very lowly paid, the changeover and the turnaround is enormous and therefore this team building is very difficult. We (the ICNA) have recently undertaken a national survey of which we have not yet collated the information, looking at standards of hygiene throughout the United Kingdom—in hospitals predominantly, and we are just getting that information together. However, it is quite surprising, just normal things like cleaning cloths are not changed every day, mops are not cleaned or washed every day. This is really a basic standard when you are dealing with an institution of sick people.

205. And also I would imagine that it is frightfully important for the cleaner to feel what an important part

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she or he is of that team, and she or he should therefore be trained to understand what effect their work can have on the health of the patient?

(*Miss Macqueen*) Yes, with the contracting out now one of the things that we do ask is what sort of training domestic services have. There is no doubt that it is inadequate by our standards and for myself I certainly insist that for the supervisor level we give quite a bit of input into their education. It is impossible to give education to all of the domestic services.

Lord Gregson

206. Is it not true that a good deal of the cleaning services are now contracted out and they are no longer the responsibility of the hospital?

(*Miss Macqueen*) Yes, it is.

207. Does this not affect the problem?

(*Miss Macqueen*) That is quite true. Although with most contracts infection control nurses have an input into the tendering exercise, and attempt to ensure that standards are included for cleaning. Because of cost this is often cut and makes it very difficult. Some hospitals have good relationships with their contractors and there are monitoring systems to make sure that the contract comes up to standard, but this is not universal.

Lord Dixon-Smith

208. Are you satisfied with the definitions in the contracts that the cleaning contractors have to provide so that the standards can be enforced if that is required?

(*Miss Macqueen*) Yes, because we lay down a standard—we being the trust—but this may be changed by managers who perceive that they have got to pay some money and there may be different levels of cleanliness. In the high dependency areas, they may say, "Yes, we need it cleaner", whereas in others they do not and this makes it very difficult for us to lay down a standard.

Lord Rea

209. I just wondered whether there is any evidence that contracting out is related in time to the rise in hospital infection, particularly resistant infections?

(*Miss Macqueen*) My Lord Chairman, I think that it is quite difficult to say that it is the cause. It certainly happened at the same time, but I would not like to say that it is the cause. There is no doubt that on investigating some outbreaks it has been a cause; a low standard of hygiene in hospital has been associated with the spread of infection.

Baroness Masham of Ilton

210. My Lord Chairman, I just wondered what happens with the private sector. There are an awful lot of untrained people used there, dressed up in smart uniforms with no training, and patients do not know: if a nurse is dressed up in uniform, they think that they are a trained nurse. There is the number of **agency**

nurses that go round from National Health Service hospitals to private hospitals, and I was talking to one who is Australian and she said she was only given by her agency one uniform and she had queried that, so I wondered what you thought about that?

(*Mrs May*) My Lord Chairman, I think that one of our greatest concerns in infection control nursing is the significant rise in the use of agency staff across all sectors of health care, and it is true to say that they do work out in the community in nursing homes; they then come and do a shift in hospitals and they may well wear exactly the same uniform from one environment to another, although I think that it is also true to say that uniforms have never been implicated in cross-infection per se, although we do know that uniforms will harbour micro-organisms. However, only in the operating environment have they been shown actually to cause infection. Standards of training and education for agency nurses are also very variable, and a lot of us are now finding that we cannot even get agency nurses, let alone full time staff.

Chairman

211. Are there special problems with **high dependency units** such as neonatal and the intensive care unit?

(*Miss Macqueen*) Yes, my Lord Chairman, one of the difficulties here is the urgent need to carry out care for the patient or child and there is a lot of to-ing and fro-ing and running around and forgetting about basic infection control measures because the life of the person is deemed to be, quite naturally, more important than worrying about cross-infection at the time. There is often overcrowding in the units unfortunately. In the United States they have demonstrated that in an intensive care unit, beds 12 feet apart are conducive to infection control. We very rarely achieve that in this country. The other aspect is the invasive devices such as intravenous infusions and the catheters that these patients have. There is much more handling and therefore they are much more at risk of cross-infection.

Lord Gregson

212. I understand that higher standards in America are more due to **litigation** than they are to hospital control. I should have thought that hospital trusts and health authorities, considering the enormous rise in the costs of litigation in the United Kingdom, would be somewhat concerned at the mass of litigation that comes out of infection from these diseases in hospital. It could be absolutely crippling?

(*Mrs May*) My Lord Chairman, I think that it is true to say that for a lot of us our experience is that managers within hospitals have been slow to recognise the risk management implications of infection control. They are becoming more aware now because of the significant rise in incidence of multi-resistant organisms, and also the general public are very much more aware now through the significant rise in media interest—and a lot of the sensationalist reporting does not help—and we are having a tremendous increase now in patients actually complaining through the

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patient complaints procedure about infections that they have acquired in hospital, and this is definitely becoming more and more common.

Lord Dixon-Smith

213. In paragraph 3.3 of your paper you say: "The problems associated with the control and management of multi-resistant organisms in the community setting make it imperative that **community infection control** service requirements are examined and adequate provisions are made to provide an effective service." What would an effective service in the community consist of and what would it cost? Dr Mayon-White we have already heard on this subject and he commends the establishment of community infection control teams. How widespread are such teams across the United Kingdom and are they cost effective?

(*Mrs Lewis*) My Lord Chairman, I believe that it is worth mentioning the change that has occurred in the set up for infection control. If we go back before the development of trusts, an infection control nurse in a district would have responsibility for hospital and community. In this situation what tended to happen was that much of the urgent work was in hospital, so that would take a great deal of your time, and only if a problem arose in the community would you actually get involved. There was very little time for proactive work in the community. With the changes that occurred and the necessity for community trusts to have in place infection control arrangements, they began to employ people specifically for that role and also consultants in communicable disease control realised the need to have infection control support in the community for the public health, so our role has actually developed. As to whether it is effective, how it should have developed, in hospital we had guidance from the Cooke Report, *Hospital Infection Control*, which recommended that you should have a doctor, a nurse, so many beds to each unit, but in the community there is no such guidance. It has occurred as and when people have felt that they have been able to afford infection control teams, where they had problems and they had to provide one, or you had a far seeing consultant in communicable disease control or infection control doctor in the community trust who said, "We must have this in place", because, as I have said, it is a proactive service. Very little has been done in the community in the way of infection control. As I said, it tended to be response to problems. Therefore, within the community the sorts of things that you need for an effective service are, we need to be able to assess the risks and the needs in the various specific settings that care is given and these can be as varied as GP practice, nursing and residential homes, community hospital settings, mental health, learning difficulties; that could be in group homes, that could be in care institutions, that could be in day centres, and that hardly touches what goes on in the community. Many clinics are being set up in the community, minor surgery is being established in a big way in GP practice. Nobody has actually looked at the risks of what needs to be in place in these areas. We need for the community, as Dr Mayon-White said, prevention

and control strategies and we need to be able to give people infection control guidelines and policies, or help them to develop their policies, because it is not something that they have had the experience with or where they have had the knowledge to be able to set it up themselves. It is also about setting standards in the community. If I may take the example of minor surgery, my Lord Chairman, many general practitioners to be able to go on the minor surgery list have to have been practising the types of surgery, but no thought has been given to what you need to be able to do it, where should it be done, what equipment should you have, how do you provide that equipment, who is going to provide it, how do you prevent infection occurring, so that falls to community infection control to look at this. We need to monitor and evaluate everything that we suggest. Is it effective in the community? It might work in the hospital—we know the things that work in hospital, but will they work in the community settings? It is also about raising the level of knowledge and awareness of infection risks. It is as if, if you move away from the acute area, perhaps the problems of infection are not seen as so acute and therefore perhaps the thought given to preventing infection needs to be input at this level. Within the community it has got to be a team approach. It has also got to be about giving people skills to be able to do it themselves because we are very few on the ground and it is a very wide area to cover. It is about educating people and it is about giving them policies, and it is about teaching them to self audit themselves, to raise their standards. The whole purpose of this, particularly with methicillin resistant *Staphylococcus aureus*, is that we are trying to protect the hospital from sending in people that have acquired methicillin resistant *Staphylococcus aureus* through their contacts in the community, because people have a lot of contact in these settings. They can pick up, they can colonise themselves with these organisms. If they go back into hospital, that is when it is a problem because you are introducing it to at risk people. It does not actually cause a great deal of problems to the healthy population and to the population that we have in the community, but we are trying to protect those in hospital who are very much at risk.

Lord Gregson

214. I am concerned about the increased use of nursing homes and residential homes and, of course, the accent that this Government are putting on care in the community as a solution to the so-called bed blocking situation which means that you are going to get a lot more transfers direct from hospital back into the community. This seems to me to be a source, this transfer from the hospital to the community, it is almost direct, is it not?

(*Mrs Lewis*) Yes, that is right. If the basic standards within the setting into which you are going to put them are not in place you will get the problems, and this is what the proactive work is trying to work out and deal with, the prevention side.

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215. What is your solution to the control of infection in these nursing homes and residential homes, and in the home itself, of course?

(Mrs Lewis) If I could take what was done locally in Worcester which is not reflected across the country, my Lord Chairman, we have been in a very privileged position. I work for a consultant in communicable disease control with vision and we have been allowed to look at the areas that we feel need to be developed. What we have done with our nursing homes and with our residential homes is to take one senior member from each of these homes and offer them training so that they can give basic advice and do the education within the home and they can self audit themselves to raise the standards. If I may answer your question as to whether we can show that there is any evidence that this is working, what happens within our own area is that they deal with patients with methicillin resistant *Staphylococcus aureus* without a problem. There is no delay in patients being transferred into care in the community because people feel comfortable, they know what they can do and it is not going to be a hazard to themselves, the staff that have to deal with it, the cleaner that has to deal with the problem as well, so it has prevented that problem. We are also seeing that it is raising the general standards within the homes. We do not get the big outbreaks now. We hear when there are one or two with a problem rather than that there are 50 in a home with a problem, so it does work.

216. But that is all voluntary, is it not, other than the threat of litigation, of course?

(Mrs May) My Lord Chairman, can I add my experience here which is totally the opposite of Joan Lewis's, and I am almost afraid to talk about it because I have told you where I work! We have a totally different situation in Nottingham where we actually do not have any community infection control nurse at all. We do not have a public health nurse for the health authority either. We also do not have infection control within the community trust's contracting and therefore the community trust do not see it as being particularly necessary because it is not specified within their contract and therefore they do not see the need to provide it. We have a situation where it is perceived that the hospital infection control nurses will provide the infection control service to the community, which is inappropriate in that my scope of professional practice as a qualified nurse gives me the right to practise in an area in which I feel competent. I have worked for 27 years in a hospital environment. I am not competent to work within a community environment and provide guidance and advice. That is the same with all my colleagues working within the hospital service in Nottingham.

217. I think the finance director of the hospital trust would have something to say about providing care in the community!

(Mrs May) Exactly, it is the vicarious liability aspect as well which does not provide me with the right to give that advice, but it is very, very difficult when somebody from a nursing home 'phones up or a member of the public 'phones up or a patient 'phones

up and says, "Can you tell me what I should do about this?", and I have to say, "I am very sorry, I cannot", and refer them to my consultant in communicable disease control.

Baroness Masham of Ilton

218. May I ask one further question because of your interest in tuberculosis. If one was flying, what is the risk of **tuberculosis** being circulated in that sealed area with air conditioning?

(Mrs Lewis) This has recently been looked at, the potential risk for this to happen, and what the team that looked at it said was that while the aircraft is in the air you have excellent ventilation which is going to reduce the chance of tuberculosis spreading. It is the time that the aircraft spends on the ground, people sitting and waiting with no ventilation running, that would be the potential risk. Having worked in the arena of tuberculosis for many years, I can say that it is not easily transmitted: you need close, prolonged contact with someone, you need someone who is going to cough over you and transmit the infection. It is certainly not one of the more easily acquired communicable diseases. Would my colleagues agree?

(Mrs May) Yes.

(Miss Macqueen) Yes.

219. You say in your paper in paragraph 4.44, that **methicillin resistant Staphylococcus aureus** appears to be increasing, and your paper paints a gloomy picture of the prospects of control. Would you please comment on the new draft national guidance on MRSA which is currently being circulated by the Department of Health, the Hospital Infection Society and BSAC? Are they a strategy for victory or for managed defeat? You also say in paragraph 4.23 of your paper that the national guidelines will recommend widespread screening of patients and staff for MRSA colonisation. While this is evidently desirable, is it practicable? You observe that a patient colonised with methicillin resistant *Staphylococcus aureus* may be at large in a hospital for two to three days before screening reveals their condition. In practice, what can be done about this? In addition, what can be done with staff who are colonised?

(Mrs May) My Lord Chairman, I am sorry that you think our paper painted a gloomy picture. It certainly was not intended to be gloomy, rather, it was intended to be realistic. Rather than seeing it as a strategy for victory or managed defeat I would like to think that it was a strategy for optimum control—or certainly that is what we perceive the guidelines to be. I would just like to comment, my Lord Chairman, on the fact that the Infection Control Nurses Association is also a contributing member to the working party. There are two infection control nurses on the working party as well. The guidelines are very eagerly awaited as an attempt to standardise practice. One of the biggest problems is that there is currently a widespread consultation exercise under way to attempt to get a consensus on the practicalities of the application of the guidelines, and that unfortunately is holding up their ultimate publication because, as Dr Mayon-White

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mentioned earlier, we do not have a national strategy and there are differing opinions among the experts as to how methicillin resistant *Staphylococcus aureus* can be optimally managed. The guidelines themselves contain some very important and useful issues, particularly the idea of risk assessment, although there is some concern that assessing the risk of a patient dependent on the clinical area in which they are cared for may cause confusion when patients move across areas. If you take an elderly patient who may be assessed as being at minimum risk in a health care of the elderly ward, he may then go to a trauma orthopaedic ward when he is assessed as being of medium risk and he may require vascular surgery where he then becomes high risk—how do we explain to his relatives, and to him himself, that he is being cared for in a different way in a different environment within the same hospital? Therefore, there may be some problems there. The guidelines will require comprehensive training and writing of local policies which obviously do have resource implications for us, but we are all very prepared to put up with those resource implications, I think. We also very much like the introduction of categorisation of recommendations. Most of the recommendations are categorised as category two, which implies consensus of expert opinion, and that is incredibly important for us in terms of implementation. It will allow us, we hope, to standardise practice not only at the local level but across regional levels because, of course, we are all taking patients from very much further afield now than within our own local hospitals. The last very useful addition to these new guidelines—which, of course, are a revision of the 1990 guidelines—is that we unfortunately now find ourselves in the position of having endemic methicillin resistant *Staphylococcus aureus*, in other words, MRSA that is there constantly in an environment, so we now have a category where hospitals can manage methicillin resistant *Staphylococcus aureus* where it is perceived to be endemic. In other words, it is not a case of using the guidelines when you have a problem; it is using the guidelines constantly because you are constantly perceived to have a problem. This will be very helpful for us, especially the risk assessment stratification, and it also goes one step further and categorises the use of isolation wards as a category one, which is at the highest standard, and that is incredibly important for us because most of us, myself included, have lost our isolation wards in the last five or six years. They no longer exist. This was because they were no longer cost effective to run and unfortunately most of us lost them before we got epidemic strains of methicillin resistant *Staphylococcus aureus*, and now it is too late to get them back again.

220. Would a national strategy help you in Nottingham? Would it put pressure on your health authority or your trust to do more?

(Mrs May) My Lord Chairman, it would not need to put more pressure on my trust because my trust is very forward thinking. The problems are across the care providers. These guidelines, of course, would not apply to the community setting. The community

setting already has its own national guidelines which were issued in 1995, but again they are only guidance. They are expert guidance, but they do not have to be formally complied with, and that is the problem.

Lord Walton of Detchant

221. In your evidence you said that the current working party guideline advises that staff be suspended from work for 24 to 48 hours if they are MRSA positive in order to receive Mupirocin treatment, but then you went on to say that there have been situations where **staff who were MRSA positive** were compelled to remain on duty. Surely there must be some legal implications of that decision?

(Mrs May) My Lord Chairman, this was from my colleague's work that she did for her master's degree when she was looking at staff perceptions of colonisation with MRSA and she presented this at our national conference last month. There was tremendous concern from amongst ourselves as professionals about the way the staff's perception of risk is so negative. Certainly, however, so far as colonised staff are concerned it depends very much on the site of the member of staff that is colonised, how big a risk there is of spread from that site and also the environment within which the member of staff is working. If you have a nurse that is working in a high dependency unit which is a very high risk unit for patients acquiring infections with methicillin resistant *Staphylococcus aureus*, not just being colonised, then I think that it is true to say that most nursing staff, and medical staff, would be encouraged to stay off work for at least the first 24 hours of Mupirocin treatment if they had nasal carriage. Nasal carriage and skin carriage in the absence of chronic skin lesions tend to be transient. The big problem is with members of staff who have chronic skin conditions such as eczema or dermatitis, which, of course, in itself may be occupationally acquired and may purely and simply be the results of having to use for long periods of time very **substandard soaps** to wash their hands with, and this comes back to the contracting of environmental cleaning because most domestic staff are responsible for purchasing soap and in order to cut costs a lot of domestic staff budgets will purchase substandard soap. We are trying to increase compliance with hand washing, which then of course has an adverse effect on staff's hands. Therefore, if you have staff with anything like chronic lesions they then can be very much at risk of becoming chronically colonised with methicillin resistant *Staphylococcus aureus*, and that is a very, very real problem.

222. What about **screening**? Do you screen your patients coming from other hospitals?

(Mrs May) Yes, in the new guidelines screening will be recommended and the guidelines will be recommending what most of us are already doing anyway. The greatest difference may well be seen in the amount of admissions screening that is recommended because at the moment we do not all routinely carry out admission screening into our trusts. However, many of us do get unacceptable requests for

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pre-discharge screening when nursing homes will not take patients unless they have a negative screen. That obviously holds up our transfer of patients and subsequently bed activity. This is not recommended in the guidelines, and that will be very useful for us as well. If I may just now go on to your final point, which was observing that a patient colonised with MRSA may be at large in a hospital for two or three days before screening reveals their condition. In practice what we all do where it is feasible to do so is to recommend isolation in a single room while we are awaiting the screen results for these two or three days, or what I call "controlled positioning", which is that we put them in a corner bed where you might only have a patient on one side of them and you put them away from others who are perceived to be at risk after assessing the risks of the patients within that particular bay. In reality this can become very difficult and most of us are now starting to see again the significant problems of trying to comply with these sorts of recommendations during the **winter bed crisis**. We cannot emphasise too strongly the impact that these bed crises are having on our ability to control methicillin resistant *Staphylococcus aureus*, because the beds are not available to put the patients into effectively.

223. What about *Panorama* on Manchester the other day? That was—and this is now—four patients in a bed in 24 hours.

(*Mrs May*) Most of us are actually already doing that. I have to say that we are already doing that, and that can be very effective bed management. The very worrying part about that programme—well, I curled up when I saw it—was the nurse who stood there and said, "We cannot find a bed for this 92 year old man with chest pains", but when the other nurse turned round and said, "He has come from a nursing home and he will go back to it, therefore, he is not going to block a bed", she said, "Right, I can find him a bed now". So, in other words, if you are not going to block a bed you can be treated; if you are going to block a bed, even at 92 you are going to have to wait on that trolley a bit longer. I think as nurses we would absolutely abhor the fact that that is what we have been reduced to.

Baroness Platt of Writtle

224. Your principal recommendation in paragraph 9 is for improved epidemiological **surveillance**, and yet, as you observe, "surveillance per se is very labour intensive", and labour intensive pressures are one of your most difficult things in any case. How would improved surveillance help you in practice? You refer to a lack of computer facilities. What more could you do given better IT?

(*Miss Macqueen*) My Lord Chairman, most of us work with a list of alert organisms, ones that are easily transmissible, both in the hospital setting and in the community and one of our real concerns is the use of data to develop league tables. At the present time the current data collection methods are often inaccurate, there is no standardisation of what an actual infection

is and therefore data are not comparable at the present time. One of the other things that we would like to see is—

225. You do want to see standardisation, is that what you are saying?

(*Miss Macqueen*) I think certainly for the future, yes. At the present time it is not feasible. Many infection control nurses do not have access to a computer, and those of us that do, I could not work without mine, and with the number of cases that I have to deal with, like my colleagues, patients are in and out every five minutes in hospital, they are going from ward to ward, on average patients in my hospital are on four to six wards for the longer term patients, and you can imagine trying to track them if they are in with a multi-resistant organism. Without the use of computers I am sometimes unaware that they may be in hospital. It enables us, I think, to differentiate between hospital and community acquired infection. At the present time I do not have access to admission data unless I go to the wards and find out. If this is on the computer I can look up quickly and think, this is possibly hospital acquired, and therefore I am alerted immediately to the fact that there is a problem in an area. In many cases this may take much longer, several days or even a week, and I think that is why we prefer to have access to an IT system. The other aspect is that the infection control nurses and the microbiologists have an excellent network across the country and very, very quickly we communicate with one another if we perceive a problem across boundaries. However, it could be improved if everybody had access to e-mail, as an example, and even faxes. The Department of Public Health give us information exceedingly quickly when there is a problem and vice versa in the hospitals out in the community.

226. Would there be a necessity for training the staff concerned to be able to use the IT fully?

(*Miss Macqueen*) Yes, there is no doubt that the average nurse is not computer literate, but they are learning very quickly. The vast majority of infection control nurses have some literacy in computers, but, yes, we do run, not courses in the Association, but study days to show people how to do surveillance and hands on work with computers.

Baroness McFarlane of Llandaff

227. You say that health care staff may combine irrational fear of infection with ignorance of basic precautions while National Health Service managers may fail to appreciate the cost of poor infection control. How much impact can staff, management and patient **education** have in this field?

(*Miss Macqueen*) I think that education and knowledge is really one of our most powerful weapons, not just with the professionals but with the patients themselves and with relatives. This comes into the public health education aspect. There is no doubt that if patients understand the risk of infection and how it is spread they can gently remind the professionals what to do, such as washing their hands. I think this is something that we have certainly developed over the

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[Continued]

[Baroness McFarlane of Llandaff *Contd*]

years, obviously if patients are able, and there is no doubt in my setting, in the paediatric setting, that parents are very much telling doctors and nurses what to do in the care of their child once they have been educated.

Baroness Platt of Writtle

228. And children can say too, can they not?

(*Miss Macqueen*) Certainly, yes, they do, and they are very good to be on our side!

Baroness McFarlane of Llandaff

229. Have you any evidence about compliance though? Telling people is one thing; compliance is another.

(*Miss Macqueen*) Compliance, I am afraid, is not always as it should be. I can quote examples in my own hospital where we have audited the compliance and there is no doubt in the paediatric setting that people perceive children as being cleaner from an infection control point of view than adults and therefore they do not see the necessity always to wash their hands each time that they are caring for a patient. There is no doubt even with parents sometimes—and I am sure that many of you have children—they do not perceive that a child can acquire an infection and be seriously ill, even things like HIV, although we are not talking about that. People do not realise that you see that in children as well.

230. And this will go for all grades of staff, doctors and nurses equally?

(*Miss Macqueen*) Yes, I am talking about a culture at the moment in hospitals and in the community. If you take post-war, people knew about hygiene and washing their hands and clean food and clean surfaces. Now people do not perceive it in the same way. You see people eating in dirty areas, children on the floor. They do not see it in the same way. As regards education, despite education staff still feel very guilty when an infection occurs, whether it is to them or to the patient. There is no doubt that they are very concerned about it. We do a lot of induction courses. I would say that medical staff lack induction courses with education on infection control. There is a perception that they should know and, in fact, they do not along with our nursing colleagues. Education does reduce fear and parents who have seen the media hype of methicillin resistant *Staphylococcus aureus*, if you go and talk to them and explain, it takes on a new light to them and I think it is educating the general public as well as the profession.

231. In the context of methicillin resistant *Staphylococcus aureus* you report that staff found to be colonised are being refused jobs and patients are being turned away from **nursing homes**. Are these problems of education, and how can they be addressed?

(*Mrs Lewis*) My Lord Chairman, I think that it is partly about education, but it is also about communication and using expert advice. If people were to ask about the appropriate placing of staff the

advice is available, education is available. Nursing homes have a problem in that they perceive that they run the risk of litigation if they take people with MRSA, they worry that their insurance premiums may go up, because they are afraid that somebody that gets MRSA in a nursing home might well sue, so that is a problem for them to get round that issue. It was taken up nationally and advice was given at the Department of Health level. I think that it is true to say that if nursing homes continue to refuse MRSA they are going to run out of patients before long! That is an issue that they are thinking about. It is education, it is communication that is so important. Another big problem in the nursing and residential home setting is that you have untrained staff in large numbers. All residential care staff are untrained with regard to nursing. In nursing homes you can have one trained member of staff on per shift being all that is required, so you are actually using people who have not a great deal of nursing knowledge and have not a great deal of knowledge of how to protect themselves or patients from transmission and their response to methicillin resistant *Staphylococcus aureus* has been what they have seen in the media—alarmist, irrational—and that is very difficult to deal with. Education is not just the simple answer; you really have to persuade people that they are not at risk.

Baroness McFarlane of Llandaff

232. Do purchasers take sufficient account of the significance of resistant infections and infection control in making **purchasing decisions**? You say in paragraph 3.2 that “the majority of infection control teams ... do not have formal contracting arrangements with their purchasers”. Does this matter? You continue, “The vast majority of infection control teams in acute hospital trusts have no budgets whatsoever”. What practical difference would it make if infection control teams had their own budgets?

(*Mrs May*) My Lord Chairman, in the past—and I think that Dr Mayon-White alluded to this in his presentation—there has been great pressure to decrease waiting lists and increase the throughput of patients to the detriment of infection control measures, amongst others. The priority of purchasers has been numbers, not quality of care. However, that is changing. There is now far more emphasis being placed on outcomes and clinical indicators. Infection control can have a significant impact on adverse outcomes such as hospital acquired infections, so purchasers are becoming more aware. Again, there is a certain element here of how much input there is from the infection control teams into purchasing decisions, in particular the role of the consultant in communicable disease control. The reason that we made the point about formal contracting is that formal contracting enables infection control teams to negotiate resources and strategies for prevention and control. If a requirement for infection control advice is not placed into a contract, then providers are at liberty to ignore such needs on the basis that if they were significant they would be there in the contracting. This is often the case, as it is in Nottingham unfortunately,

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[Continued

[Baroness McFarlane of Llandaff *Contd*]

in community trusts and we are not saying that they necessarily require a specific infection control nurse, we are not saying that; what we are saying is that they should have access to expert guidance, education and training and experts to provide them with the policies and procedures that they need to implement adequate infection control. The priorities and planning guidance for 1997 and 1998 issued by the NHS Executive does require directors of public health to ensure that adequate provision is made for infection control, and the easiest way to do this is through formal contracting arrangements. The other issue that we find in hospitals, my Lord Chairman, is that often the purchase of infection control service is incorporated into the microbiology or the Public Health Laboratory Service contract. It is not separated out, so you purchase a service which is the entire diagnostic microbiology service and it also includes the purchase of the infection control service but it does mean that there can be virtually no resourcing within the trust for infection control because it all goes on diagnostic microbiology and this obviously makes it very difficult for us to identify resources such as computer facilities. Therefore, my Lord Chairman, budgets themselves

—and we are not looking for huge sums of money, we are just looking for small sums of money so that we are then able to purchase with those small sums of money IT equipment and resources such as the personnel to input data, secretarial time so that we are not spending significant amounts of our time actually writing up the policies and the procedures which is a very great waste of our time and the money that the trusts are paying us to do what is in effect an administrative and clerical job. It also would enable us to purchase maybe additional research nurses, not highly qualified infection control nurses, to undertake the surveillance, the number crunching, the surveillance and audit. It would also enable us to purchase what at the present time most of us beg, steal and borrow by whatever means we can, things, commodities, like stationery: you hope that the chief

executive's stationery cupboard is open when you walk past and you can pinch a box of photocopying paper because we do not have a budget to purchase our own, that sort of thing.

Baroness McFarlane of Llandaff

233. Can you point to any examples of best practice?

(*Mrs May*) What we meant by the statement—because it was one of our recommendations—was that we would welcome a commitment to auditing against minimum standards through the contracting process, and this could be measured in a number of ways, but particularly through accreditation, which of course is very big in the United States, as I am sure those of you who are going to the United States will find out. A good example in the United Kingdom is the King's Fund organisational audit which has a big chapter on infection control in it, and such minimum standards would include availability of policies and procedures, compliance with them, adequate isolation facilities, targeted surveillance, adequate resourcing of infection control and standard setting, those sorts of minimum standards which we should all be working to.

234. With respect to accreditation in the United States, is there a state accreditation or is it a national one?

(*Mrs May*) My Lord Chairman, I think that most of the hospitals—and I may have got this wrong—comply with the JCAHO accreditation, which is the Joint Committee of Accreditation in Healthcare Organisations. I think that is what it stands for. That is the accreditation that they have to comply with to enable them to get their funding through their insurers.

235. Thank you very much for coming along and also for the documentation that you have provided to the Committee.

(*Mrs May*) Thank you very much, my Lord Chairman.

TUESDAY 4 NOVEMBER 1997

Present:

Dixon-Smith, L.	Platt of Writtle, B.
Jenkin of Roding, L.	Porter of Luddenham, L.
McFarlane of Llandaff, B.	Rea, L.
Masham of Ilton, B.	Soulsby of Swaffham Prior, L.
Perry of Walton, L.	(Chairman)

Memorandum by Dr P Davey, Ninewells Hospital and Medical School

**COSTS OF ANTIBIOTIC RESISTANCE IN HOSPITALS AND PRIMARY CARE:
RECOMMENDATIONS FOR POLICY CHANGE AND RESEARCH**

1. EXECUTIVE SUMMARY

1. the risk of infection by antibiotic resistant bacteria depends on three main factors:

- (a) The patient.
- (b) The setting.
- (c) The antibiotics prescribed to the patient *but*:

Antibiotics are only part of the problem;

- It is relatively easy to show that withdrawal of an antibiotic is one of the factors which helps to control an outbreak of infections caused by drug-resistant bacteria;
- It is much more difficult to show that tight control of antibiotic prescribing prevents the occurrence of antibiotic resistance.

2. Antibiotic resistance is only one manifestation of the harmful effects which antibiotics have on the human microbial flora. Professionals and the public would benefit from education about:

- (a) The important functions of the bacteria which normally colonise humans and the fact that most of them never cause infections.
- (b) The unpleasant consequences of replacement of the normal flora by other micro-organisms.
 - Normally pathogenic bacteria (e.g., *Streptococcus pyogenes*).
 - Bacteria which rarely infect patients unless they have received antibiotics (e.g., *Clostridium difficile*).
 - Fungi and yeasts (e.g., *Candida albicans*).

3. Costs of antibiotic resistance fall on:

- (a) The index case:
 - Slower response to antibiotic treatment.
 - Increased morbidity and mortality from infection.

However:

Some patients get better despite receiving the wrong antibiotic.

Some patients do not get better despite receiving the right antibiotic.

Nonetheless, the right antibiotic tips the balance of probability in the patient's favour.

(b) Other patients:

- Inadequate treatment of the index case increases the risk of spread of infection to other patients, especially in hospitals.
- Concerns about resistance may result in prescribers selecting antibiotics which are actually less effective against sensitive bacteria than the drugs that they replace, or that have more adverse effects on the patient or the patient's flora.
- Infection control measures include closure of wards, cancellation of operations, delaying treatment of other patients.

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- (c) The NHS:
 - Overcoming resistance usually requires new antibiotics which are more expensive than the drugs that they replace.
 - Control of outbreaks of infection caused by antibiotic resistant germs imposes additional costs.
- (d) Society:
 - In the antibiotic era, developed countries have become complacent about the divesting socio-economic effects of infections.
- 4. Policies for limiting the spread of antibiotic resistance in hospitals have been set out in detail by consensus groups in the USA;
 - (a) These are based in part on strategies for early streamlining or termination of unnecessary antibiotic treatment.
 - (b) They would be difficult to implement directly in the UK because of relatively poor hospital information systems.
 - (c) Nonetheless, some practical targets for implementation and audit in the UK could be defined, notably for surgical prophylaxis.
- 5. We currently spend more money on the antibiotic treatment of patients who do not have proven bacterial infections than we do on patients with proven infection.
 - (a) The solution is to develop standards for the duration of antibiotic prophylaxis or treatment.
 - (b) Once standards have been developed, audit of practice and behaviour change are possible.
- 6. Policies for limiting the spread of antibiotic resistance in the community are less well defined.
 - (a) There is limited evidence linking antibiotic resistance to *community* prescribing.
 - (b) There is considerable variation in prescribing rates between different practices.
 - (c) There is evidence that training practices prescribe more conservatively than non-training practices.
 - (d) The most persuasive evidence would be to show that reduction in antibiotic practice leads to a decline in antibiotic resistance.
- 7. Restrictive antibiotic policies raise legal issues:
 - (a) Is a policy acceptable if it puts some patients at risk in order to preserve a resource for other patients?
 - (b) Would restricting antibiotics be more acceptable if the primary aim was to protect the normal flora of the patient who would have received antibiotics?
 - (c) What evidence is required to justify restrictive antibiotic policies? Is the opinion of the local policy makers sufficient?

Recommendations for policy and research

TABLE 1

Evidence in support of a link between antimicrobial prescribing and the prevalence of drug resistant strains of bacteria, with some of the potential confounding variables which could mean that it is wrong to interpret the association as simple cause and effect. For more detailed analysis see 1-3.

Supporting evidence	Potential confounding variables
1. In the pre-antibiotic era pneumococci and other streptococci were common causes of nosocomial infection. In the antibiotic era they have been replaced by organisms such as <i>Pseudomonas aeruginosa</i> . In general, antimicrobial resistance is more prevalent in bacterial strains causing nosocomial infection than in organisms from community-acquired cases.	1. There have been many other changes which may account for these observations (case mix, new medical technology).
2. Patients with resistant organisms are more likely to have received prior antibiotic therapy than are controls.	2. Antibiotic use may just be a marker for patients who are more ill.
3. Concurrent variation between antimicrobial utilisation and resistance has been noted for both increases and decreases in these two factors.	3a. Other reports document decreased prevalence of antimicrobial resistance without a corresponding decrease in antimicrobial use.

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[Continued

Supporting evidence	Potential confounding variables
	3b. It is difficult to separate control of antimicrobial prescribing from other infection control measures which are used in the context of an outbreak of nosocomial infection with drug resistant strains.
4. There is a dose response relationship between antimicrobial prescribing and the probability of infection with drug resistant strains which operates at several different levels (individual patient, ward unit hospital and country).	4. The association may be because of differences in underlying disease and/or aspects of management other than antimicrobial therapy.
5. Interruption of transmission of resistant organisms (e.g., barrier isolation techniques) and control of antimicrobial prescribing are the only two measures which have been shown to be successful in limiting the prevalence of drug resistant bacteria.	5. It is virtually impossible to separate the effects of these two measures, which are almost always implemented concurrently.

2. ANTIBIOTIC RESISTANCE IS ONLY ONE MANIFESTATION OF THE HARMFUL EFFECTS WHICH ANTIBIOTICS HAVE ON THE HUMAN MICROBIAL FLORA

Professionals and public require education. Germs are good for the body; antibiotics are bad for the body.

- The human body contains 10^{15} individual microbes and 10^{13} mammalian cells.
- Who is parasitising whom?
- The term parasite implies a predatory relationship, particularly in the late 20th century (“social parasites”).
- The relationship between the normal human flora and the host is complex but the majority of skin and bowel commensals never cause disease in humans.
- Removal of the relatively harmless commensal streptococci from the mouth increases the risk of colonisation and infection by *Streptococcus pyogenes*^{4,6}.
- Many hospitals are seeing an exponential increase in the incidence of antibiotic associated colitis, caused by *Clostridium difficile*⁷ (Figure 1, Page 6).
- Exposure to antibiotics markedly increases the risk of women receiving an antifungal preparation for suspected vaginal thrush (Figure 2, Page 6).

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Figure 1: Clostridium colitis at Oregon Health Sciences\VA Medical Centre

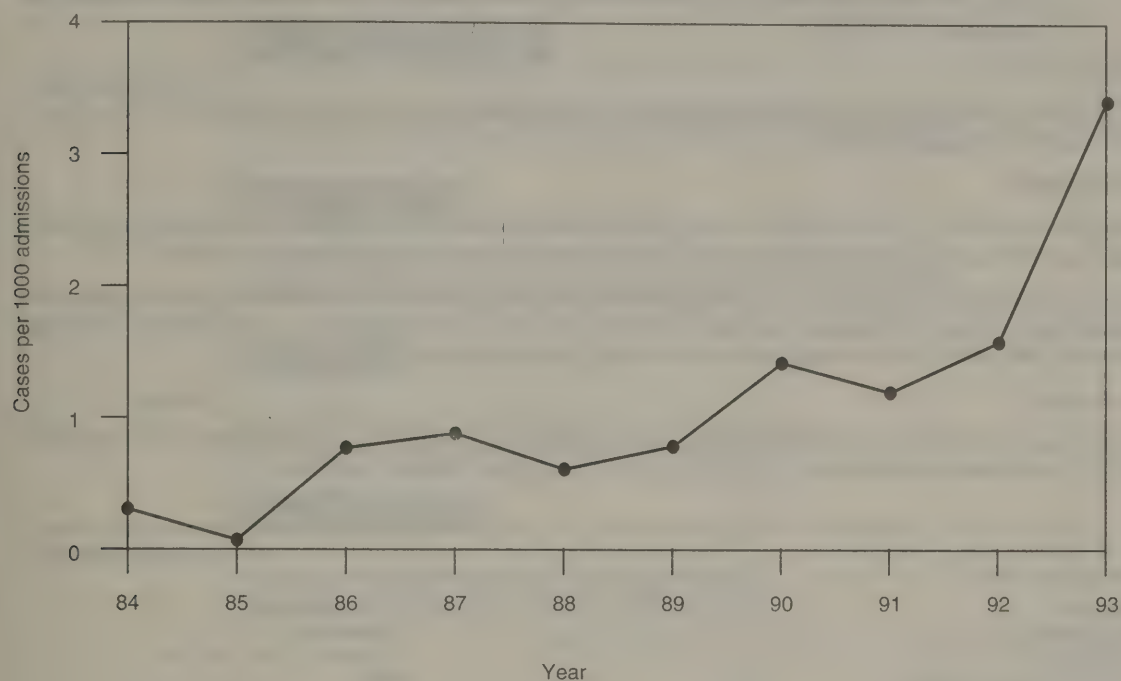
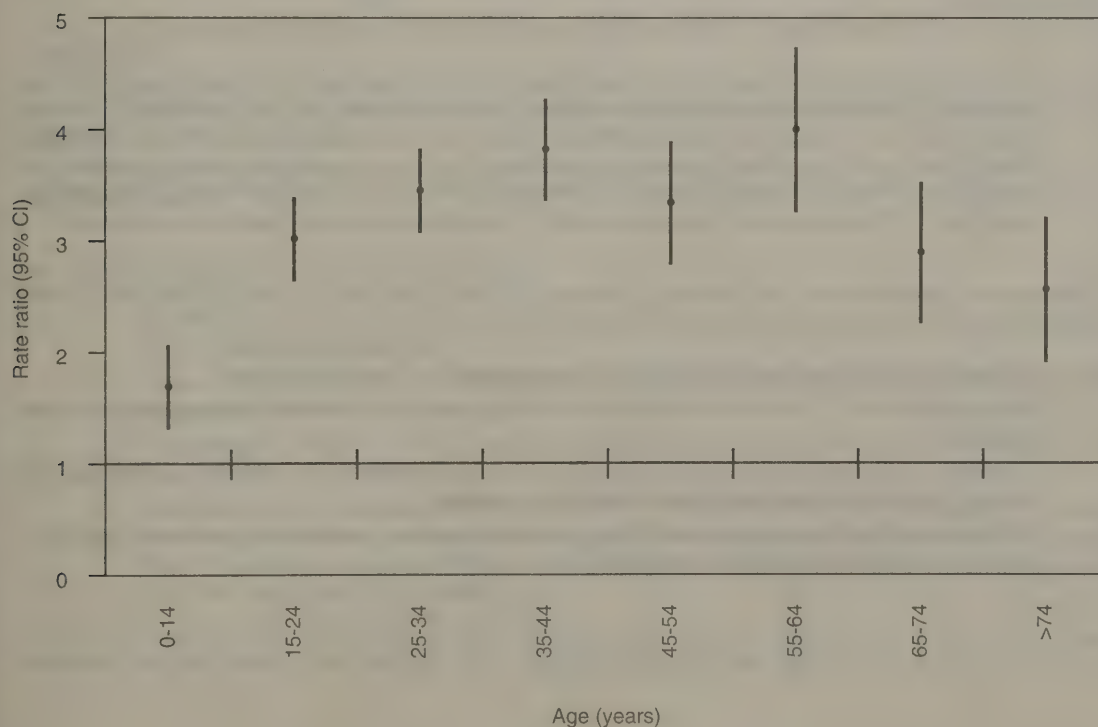


Figure 2: Increased risk of women receiving an antibacterial drug in the 28 days before being prescribed an antifungal drug, by age. The data were derived from dispensing to women in Tayside from 1 February 1993 to 31 August 1994. A total of 19,832 women who had been dispensed an antifungal drug were identified from the population of 201,000 women resident in Tayside at the time⁸.



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[Continued

3. COSTS OF ANTIBIOTIC RESISTANCE

- These are well illustrated by an outbreak of infection caused by penicillin resistant *Streptococcus pneumoniae* in Bristol:

The index case:

The patient received ineffective antibiotic therapy for his pneumonia until the resistant nature of the pathogen was identified. The patient died.

Other patients:

By the time that the problem had been recognised the infection had spread to eight other patients in the same ward, a care of the elderly unit housing patients who are very susceptible to respiratory infection.

The current generation of hospital doctors is not used to thinking of *Streptococcus pyogenes* and *Streptococcus pneumoniae* as causes of hospital acquired infection, but in the pre-antibiotic era these highly contagious pathogens were amongst the commonest causes of post-operative infection⁹.

The hospital:

Following this outbreak, mean monthly antibiotic expenditure on the unit rose nearly three-fold, from £2,887 to £7,377, and remained elevated at £4,069 per month four months after the outbreak.

*The costs of containing an outbreak of infection by drug-resistant Salmonella heidelberg have been documented in detail*¹⁰

Resources consumed

Laboratory	22 technician days
Ward closures	48 bed days
Staff absence	42 cook days 14 nurse days
Control of infection meetings	72h
Collection of specimens	50h
Hospital supplies and administration	51h

Estimated financial costs

Administration and supplies	£1,271
Investigations	£1,589
Extra staff	£4,786
Medication	£295
Microbiology laboratory	£3,970

- A less obvious cost of resistance to other patients is that the antibiotic selected to cope with the possibility of infection by resistant pathogens may be less effective than the antibiotic it replaces. Vancomycin is a weakly bactericidal antibiotic with very poor penetration into the cerebrospinal fluid. There is evidence that vancomycin is less effective than penicillin for the treatment of meningitis caused by penicillin sensitive pneumococci¹¹ and less effective than semi-synthetic penicillins for the treatment of infections caused by methicillin sensitive *Staphylococcus aureus*^{12, 13}.

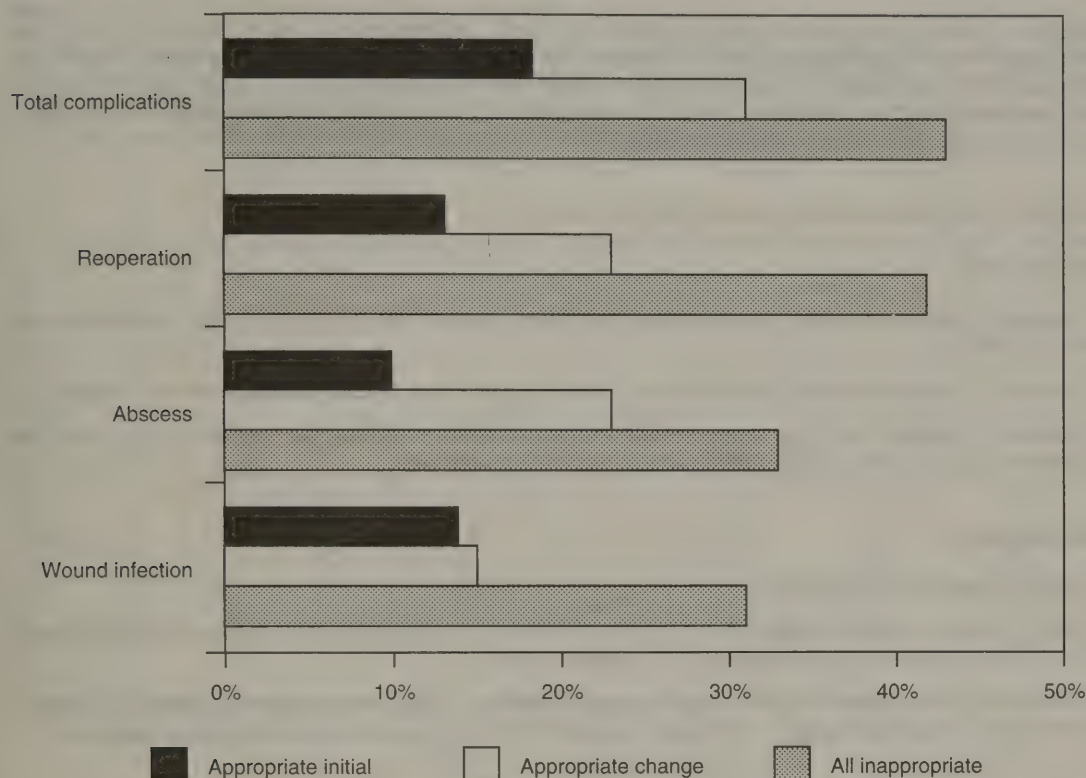
4. EVIDENCE THAT ANTIBIOTIC RESISTANCE DOES INFLUENCE THE OUTCOME OF TREATMENT OF SERIOUS INFECTIONS (DRAWN FROM DATA IN ¹⁴)

Figure 3: Outcome of surgical peritonitis stratified by appropriateness of antibiotic therapy.

- "Appropriate initial": the bacteria were sensitive to the empirical antibiotics prescribed at the time of operation.
- "Appropriate change": at least one of the bacteria was resistant to the empirical antibiotics, but therapy was changed after the culture results were obtained.
- "All inappropriate": therapy was not changed and the patient continued to receive antibiotics to which one or more bacteria were resistant.

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[Continued



Why was appropriate antibiotic treatment more effective when it was started at the time of surgical debridement?

1. Antibiotics work best against rapidly dividing bacteria and are relatively ineffective once abscess formation occurs.
2. Ineffective treatment results in uncontrolled systematic effects of sepsis, which further compromises patient outcome.

5. FURTHER IMPORTANT MESSAGES FROM THIS STUDY

- Patients who received appropriate antibiotic treatment at the time of surgical debridement still had a 19 per cent complication rate.
- Conversely, patients who continued to have inappropriate antibiotic treatment had a 44 per cent complication rate.
- Therefore the majority (56 per cent) of patients who received inappropriate antibiotics had no complication.
- These data were collected over a period of three years in five hospitals. The individual clinician treats too few cases of surgical peritonitis to assess the appropriateness of his/her antibiotic treatment based on clinical outcome and may well be lulled into a false sense of security, despite prescribing less than optimal antibiotic treatment.

Similar, large scale epidemiological studies linking data about drug resistance, antibiotic prescribing and treatment outcome would be worthwhile, both in hospitals and the community.

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6. TARGETS FOR IMPROVING ANTIBIOTIC PRESCRIBING IN HOSPITALS.

Examples of strategies to optimise the prophylactic, empiric and therapeutic use of antimicrobials in the hospital, together with suggested measures of outcome and process to be used in audit. It is unlikely that many UK hospitals have information systems which would allow easy assessment of the outcome measures, but the process measures should be achievable without too much difficulty. Adapted from more extensive tables in.¹⁵ Additional guidelines have been published recently.¹⁶

1. OPTIMISE ANTIMICROBIAL PROPHYLAXIS FOR OPERATIVE PROCEDURES

Process measures

1. Number of patients receiving inappropriate prophylactic antimicrobials as a percentage of total patients receiving prophylaxis.
2. Number of patients receiving prophylaxis for <24h as a percentage of total patients receiving prophylaxis.
3. Number of patients receiving antimicrobials within two hours preceding the surgical incision or at the time of the incision as a percentage of total patients receiving prophylaxis.

Outcome measures

1. Surgical site infection (SSI) rate.
2. Rate of SSIs occurring postoperatively in patients who receive inappropriate prophylaxis compared with the rate of SSIs in patients who receive appropriate prophylaxis.
3. Number of antimicrobial-resistant micro-organisms recovered within seven to 10 days following surgery from patients receiving inappropriate prophylaxis compared with patients receiving appropriate prophylaxis.

2. OPTIMISE CHOICE AND DURATION OF EMPIRIC ANTIMICROBIAL THERAPY

Process measures

1. Mean or median time interval between the initiation of empiric therapy and arrival at a microbiological diagnosis.
2. Number of patients with a microbiological diagnosis who are receiving inappropriate empiric therapy as a per cent of total patients.
3. Mean and or median duration of empiric therapy stratified by antimicrobial type.

Outcome measures

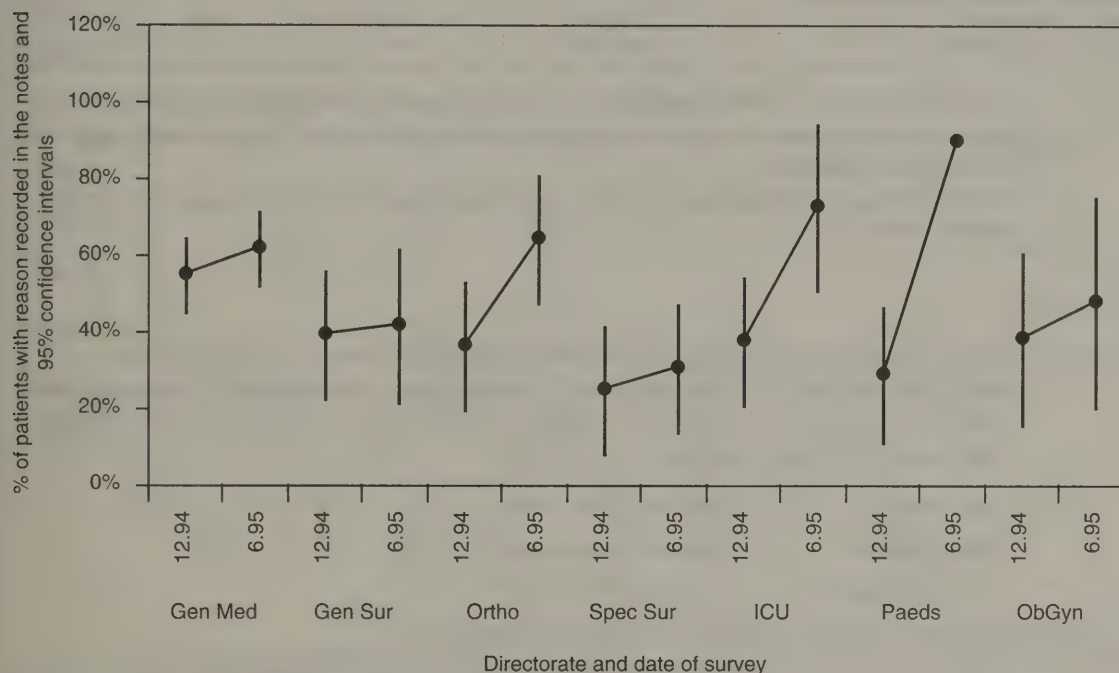
1. Number of infections due to isolate resistant to antimicrobial used for empiric therapy.
2. Number of adverse events of empiric therapy as a per cent of total patients.
3. Cost of quantity of empiric antimicrobial administered in a specified period.

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[Continued

Figure 4. Problem: Case notes do not contain enough information to assess the appropriateness of antibiotic treatment.

In Dundee Teaching Hospitals Trust less than half of the patients prescribed antibiotics have a reason recorded in the case notes. This figure shows the results of two audits of the entire Trust (three hospitals with 48 wards on two sites; 750-850 inpatients). The proportion of patients with reason for treatment recorded in the notes did show some improvement after feedback to Clinical Directors of results of the first audit.



Solution: Antibiotic stamp piloted in the Infectious Diseases Unit, and now extended to all acute admissions to the Directorate of Medicine

- Junior doctors who prescribe antibiotics are obliged to use the stamp to record a standard data set which can then be used in reviewing the clinical justification for any antibiotic therapy and for the specific regimen selected.
- The aim is to stop unnecessary antibiotic treatment as soon as possible, recognising that most treatment is started by inexperienced junior staff dealing with complex clinical cases.¹⁷
- The prototype was a rubber stamp but this was frequently lost and has been replaced by green, adhesive labels.

Antibiotic therapy

Date started:	Symptoms of infection Y/N	
Reason:	Temperature:	
Antibiotic/s:	Dose:	
Pulse:	BP:	Respiratory rate:
Route of administration:	Planned duration:	Blood cultures taken Y/N

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7. PROBLEM: WE CURRENTLY SPEND MORE MONEY ON THE ANTIBIOTIC TREATMENT OF PATIENTS WHO DO NOT HAVE PROVEN BACTERIAL INFECTION THAN WE DO ON PATIENTS WITH PROVEN BACTERIAL INFECTION.

Data on the costs of managing suspected and proven infection after surgery¹⁸

	Additional cost per patient	Per cent of patients with fever	Number with fever per 100 patients	Additional cost per 100 patients (million)
Suspected infection, unconfirmed by further investigation	\$15,000	84	84	\$1.26
Proven bacterial infection	\$45,000	16	16	\$0.72

- These data are from an audit of antibiotic prescribing to patients undergoing surgery for cancer.¹⁸
- Fever after major surgery is common and is usually due to inflammatory changes after surgery rather than to bacterial infection.
- Initial assessment of febrile patients is by inexperienced junior staff with limited data (results of bacterial culture, etc).

8. SOLUTIONS

Develop and audit standards for the duration of antibiotic treatment for common clinical problems:

- Results of setting standards for the duration of antibiotic therapy after emergency abdominal surgery in a prospective study of 163 patients.¹⁹ All patient received a single administration of antibiotics:

No further treatment	60 patients (37 per cent)
24h treatment	32 patients (20 per cent)
48h treatment	48 patients (29 per cent)
3-5 days treatment	23 patients (14 per cent)

Target expert advice at patients at high risk of inappropriate treatment:

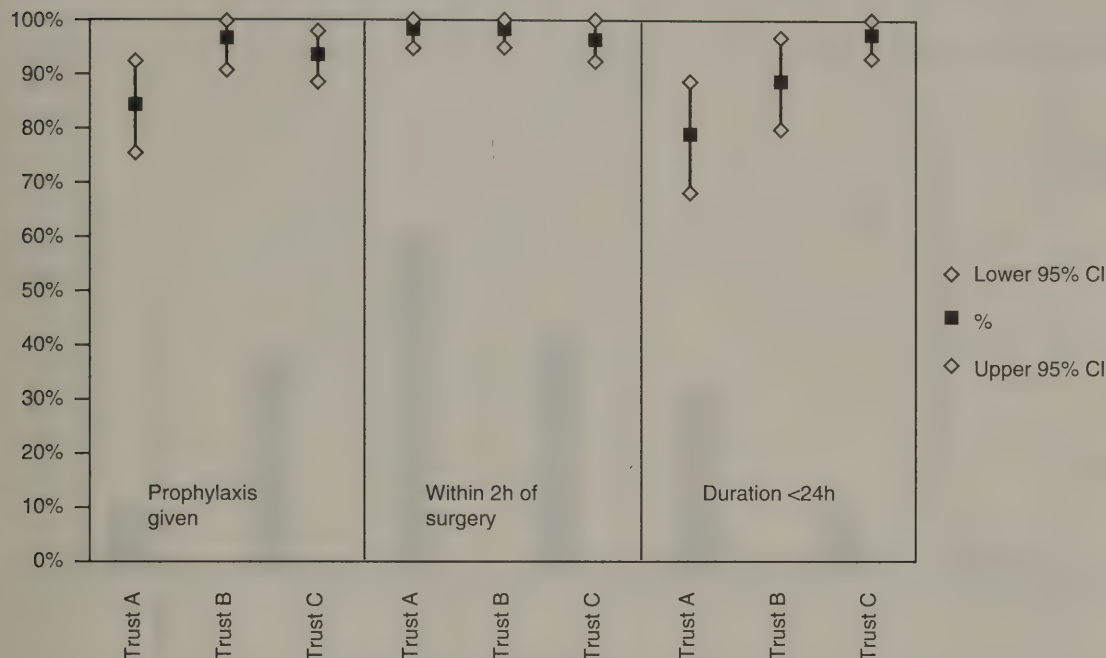
- Studies from the USA^{20, 21} and our own experience in the UK²² show that specialist review of patients with bacteremia results in identification and correction of both over-treatment of patients at low risk and under-treatment of patients at high risk.

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Compare standards in different hospitals:

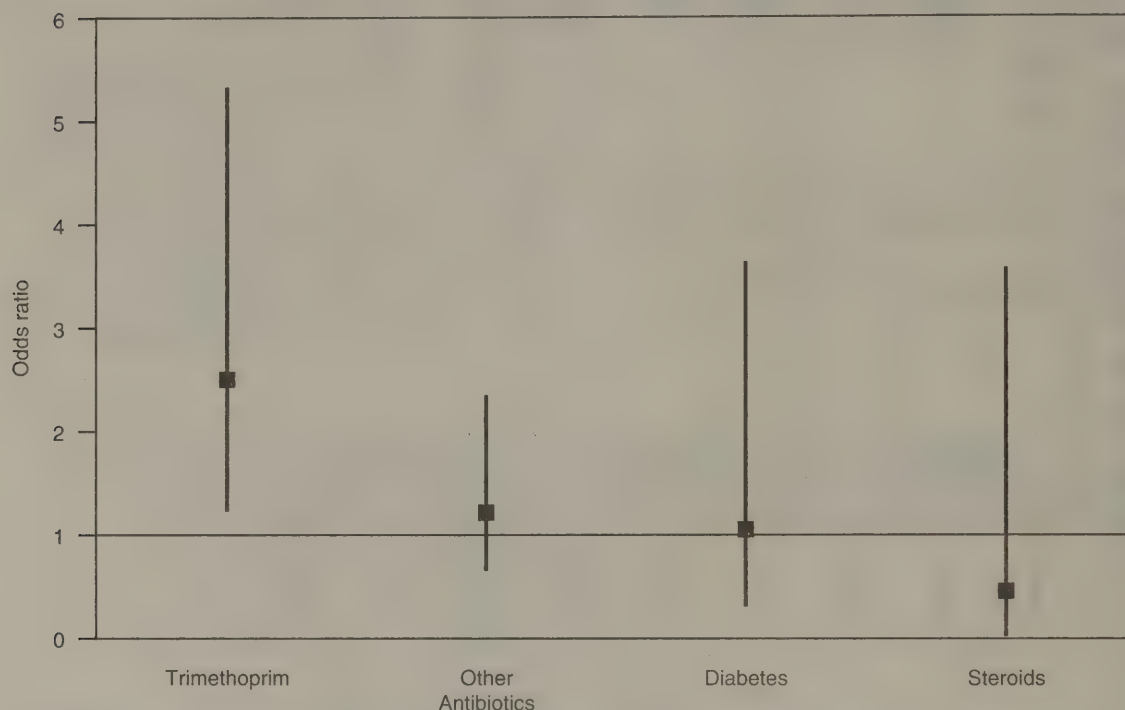
Figure 5: Data from three Acute Hospital Trusts (Dundee, Perth and Stracathro) in Tayside



- Analysis was confined to operations performed in all three trusts. The total number of operations audited was 166.
- Clinical Directors were asked to identify which operations required prophylaxis and to confirm that their policy stated that the first dose of prophylaxis should be given in theatre and that the total duration of prophylaxis should not exceed 24h.
- Marked differences were noted in achievement of two standards:
 - Prophylaxis was least likely to be administered in Trust A;
 - However, when prophylaxis was administered, it was also least likely to be stopped within 24h in Trust A.
- Nonetheless, the results in all three trusts compared favourably with recently published results from other centres.
 - Of the 293 patients who received prophylaxis, 35 (12 per cent) continued for >24h;
 - In comparison:
 - 62 per cent of patients received >3 doses of prophylaxis for general surgery or orthopaedic operations audited in Aberdeen²³
 - 23 per cent of patients received prophylaxis for >48h in an audit of practice in Belgium.²⁴

Figure 6: Evidence that community antibiotic prescribing is linked to antibiotic resistance:

People with cystitis caused by trimethoprim resistant bacteria are more likely to have received trimethoprim in the past six months than people who have cystitis caused by trimethoprim sensitive bacteria.



These data come from a pilot study in the Tayside population.²⁵

- Information was extracted from all urine samples sent by GPs to the microbiology laboratory in July 1994. The samples were classified as follows:
 - No bacteria isolated (n=52)
 - Trimethoprim sensitive bacteria isolated (n=213)
 - Trimethoprim resistant bacteria isolated (n=563)
- The MEMO prescribing database was used to extract person-specific prescribing information for the six months before isolation of the bacteria, excluding the two weeks before the sample was sent in order to exclude treatment for the current episode.
- The hospital SMR database was used to identify all hospital discharges in the previous six months.

The figure compares people with trimethoprim resistant bacteria *versus* people with trimethoprim sensitive bacteria. The same result is obtained if the control group is changed to people with no bacteria isolated.

Excluding patients who have been hospitalised in the past six months did not change the results.

Figure 7: There is considerable variation in rates of dispensing of antibiotics between GP practices in Tayside. Non-training practices tend to prescribe more antibiotics than training practices. These differences were independent of other factors such as fundholding status, age or sex of practitioners.

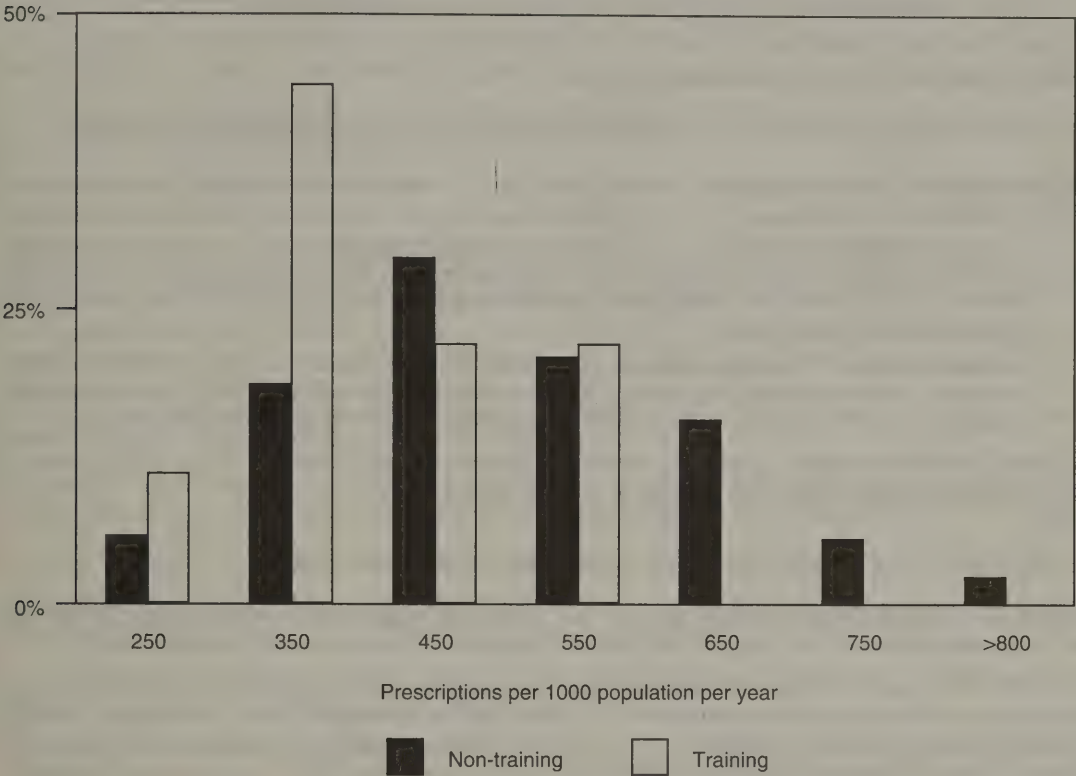
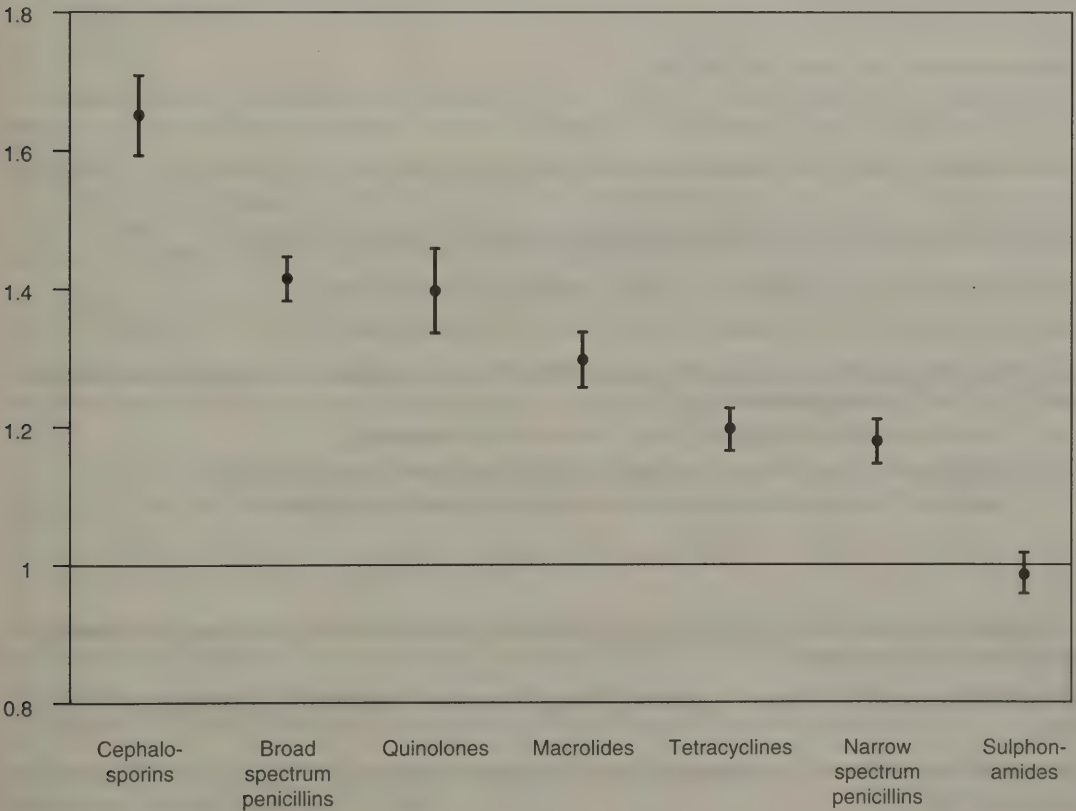


Figure 8: The difference is most marked for broad spectrum antibiotics (cephalosporins, broad spectrum penicillins and quinolones):



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This figure shows the ratio of prescribing of individual antibiotic classes for non-training practices *versus* training practices, corrected for practice size.

- The ratio for cephalosporins is 1.65. This means that non-training practices prescribe 65 per cent more cephalosporins per 1,000 practice population than training practices.

9. MEDICO-LEGAL ASPECTS OF HOSPITAL ANTIBIOTIC POLICIES

Medical practice variation between the USA and the UK: Medical practice driven by fears of litigation?

Cost of infection management reported in studies from the UK are orders of magnitude lower than costs reported in studies from the USA:

- The cost per patient treated for infection following hysterectomy was only £9 in one of our studies²⁶ because almost all infections were treated with inexpensive oral antibiotics. This is in marked contrast to a trial from the USA, which reported average excess costs of \$1,777 for patients with infection after hysterectomy.
- Similarly, Ford *et al*²⁸ report antibiotic costs of \$1,567 for treatment of patients with fever after caesarean section, compared with up to £20 in a similar study from Bristol, UK²⁹. Mean therapeutic antibiotic costs for infections complicating other elective surgery are similarly low in the UK³⁰.

It is likely that these examples of marked differences between the USA and UK in the management of suspected infection are due in large part to differences in the legal system.

10. IS THIS A REASONABLE INTERPRETATION OF THE CURRENT LEGAL POSITION IN THE UK?

In the UK there are clear legal judgments showing that a doctor is obliged to follow an accepted professional standard of practice, and that it is not up to the court to determine or comment on that standard of practice³¹⁻³³.

A UK doctor who prescribed oral antibiotics for suspected post-operative infection, or withheld prophylactic antibiotics in accordance with a local written policy is unlikely to be successfully sued for negligence, even if some experts disagree with the local policy. The court must determine whether or not the doctor followed a professionally accepted standard of practice, which does not necessarily have to be either the most frequently followed standard, or the best possible available treatment.

This is in marked contrast to the legal system in the USA, which virtually obliges doctors to use the maximum available treatment in every patient.

11. RECOMMENDATIONS FOR POLICY AND RESEARCH

Policy

1. Public education about the importance of the normal human flora and the harmful effects of antibiotics on it.
2. Adapt US guidelines for prevention of antibiotic resistance in hospitals to the UK.
3. Develop guidelines for prevention of antibiotic resistance in the community.
4. Extend provisions for involvement of general practices in training and audit.
5. Clarify the legal implications of policies which restrict the use of antibiotics in hospital or the community. The issues which need to be addressed are:
 - Not starting antibiotic treatment (most relevant in the community);
 - Early cessation of unnecessary antibiotic treatment (most relevant in hospitals);
 - Conflicts of interest between the individual patient and the public health.

Research

1. Epidemiological studies on the impact on clinical outcome of reduced bacterial susceptibility to antibiotics in hospitals and in the community.
2. Epidemiological studies in the community linking data about variations in prescribing to antibiotic resistance.
3. Collection of data about antibiotic resistance alongside studies aimed at reduction of community antibiotic prescribing.

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Bibliography

1. McGowan J E J. Antimicrobial Resistance in Hospital Organisms and Its Relation to Antibiotic Use. *Rev Infect Dis* 1983; 5, No. 6: 1033-1048.
2. Richard P, Le Floch R, Chamoux C, Pannier M, Espaze E, Richet H. *Pseudomonas aeruginosa* outbreak in a Burn Unit: Role of Antimicrobials in the Emergence of Multiply Resistant Strains. *J Inf Dis* 1994; 170: 377-383.
3. Richard P, Delangle M, Merrien D, *et al.* Fluoroquinolone Use and Fluoroquinolone Resistance: Is there an Association? *Clin Infect Dis* 1994; 19: 54-59.
4. Sanders C C, Sanders W E, Harrowe D J. Bacterial interference: Effects of oral antibiotics on the normal throat flora and its ability to interfere with group A streptococci. *Infect Immun* 1976; 13: 808-812.
5. Sanders C C, Nelson G E, Sanders W E. Bacterial interference IV. Epidemiological determinants of the antagonistic activity of the normal throat flora against group A streptococci. *Infect Immun* 1977; 16: 599-603.
6. Pichichero M E, Disney F A, Talpey W B. Adverse and beneficial effects of immediate treatment of Group A beta-haemolytic streptococcal pharyngitis with penicillin. *Pediatr Infect Dis J* 1987; 6: 635-643.
7. Jobe B A, Grasley A, Deveney K E, Deveney C W, Sheppard B C. *Clostridium difficile* colitis: an increasing hospital-acquired illness. *Am J Surg* 1995; 169: 480-483.
8. Barbone F, Steinke D, MacDonald T, McDevitt D G, Davey P G. Antibacterials and vulvovaginal candidiasis: a record-linkage case-crossover study. *Pharmacoepidemiol Drug Safety* 1997; 6: S76 (Abstract).
9. Selwyn S. Hospital infection: the first 2,500 years. *J Hosp Infect* 1991; 18 (Supplement A): 5-64.
10. Barnass S, O'Mahony M, Sockett P N, Garner J, Franklin J, Tabaqchali S. The tangible cost implications of a hospital outbreak of multiply-resistant *Salmonella*. *Epidemiol Infect* 1989; 103: 227-234.
11. Viladrich P F, Gudiol F, Linares J, *et al.* Evaluation of vancomycin for therapy of adult pneumococcal meningitis. *Antimicrob Agents Chemother* 1991; 35: 2467-2472.
12. Karchmer A W. Is vancomycin versus *Staphylococcus aureus* optimal therapy? *Infect Dis Clin Pract* 1992; 1: 143-144.
13. Small P M, Chambers H F. Vancomycin for *Staphylococcus aureus* Endocarditis in Intravenous Drug Users. *Antimicrob Agents Chemother* 1990; 34: 1227-1231.
14. Mosdell D M, Morris D M, Voltura A, *et al.* Antibiotic treatment for surgical peritonitis. *Ann Surg* 1991; 214: 543-549.
15. Goldmann D A, Weinstein R A, Wenzel R P, *et al.* Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *JAMA* 1996; 275: 234-240.
16. Schlaes D M, Gerding D N, John J F, *et al.* Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Clin Infect Dis* 1997; 25: 584-599.
17. Isaacs D, Wilkinson A R, Moxon E R. Duration of antibiotic courses for neonates. *Archives of Disease in Childhood* 1987; 62: 727-728.
18. Shulkin D J, Kinosian B, Glick H, Glen-Puschett C, Daly J, Eisenberg J M. The economic impact of infections: an analysis of hospital costs and charges in surgical patients with cancer. *Arch Surg* 1993; 128: 449-452.
19. Schein M, Assalia A, Bachus H. Minimal antibiotic therapy after emergency abdominal surgery. A prospective study. *Br J Surg* 1994; 81: 989-991.
20. Horn D L, Opal S M. Computerised clinical practice guidelines for review of antibiotic therapy for bacteremia. *Infect Dis Clin Pract* 1992; 1: 169-173.
21. Dunagan W C, Woodward R S, Medoff G *et al.* Antibiotic misuse in two clinical situations: Positive blood culture and administration of aminoglycosides. *Rev Infect Dis* 1991; 13: 405-412.
22. Nathwani D, Davey P, France A J, Phillips G, Orange G, Parratt D. Impact of infection consultation service for bacteremia on clinical management and use of resources. *Quart J Med* 1996; 89: 789-797.
23. Gould I M, Jappy B. Trends in hospital antibiotic prescribing after introduction of an antibiotic policy. *J Antimicrob Chemother* 1996; 38: 895-904.

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24. Kurz X, Mertens R, Ronveaux O. Antimicrobial prophylaxis in surgery in Belgian hospitals: room for improvement. *Eur J Surg* 1996; 162: 15-21.
25. Steinke D, Seaton A, Phillips G, MacDonald T M, Morris A, Davey P G. Impact of community antibiotic prescribing and hospitalisation on the risk of urinary tract infection with drug-resistant bacteria: a case-control study. *Pharmacoepidemiol Drug Safety* 1997; 6: S80(Abstract).
26. Davey P, Duncan I D, Edward D, Scott A C. Cost-benefit-analysis of cephadrine and mezlocillin prophylaxis for abdominal and vaginal hysterectomy. *Br J Obstet Gynaecol* 1988; 95: 1170-1177.
27. Shapiro M, Schoenbaum S C, Tager I B, Munoz A, Polk F. Benefit-cost analysis of antimicrobial prophylaxis in abdominal and vaginal hysterectomy. *JAMA* 1983; 249: 1290-1294.
28. Ford L C, Hammil H A, Lebherz T B. Cost-effective use of antibiotic prophylaxis for cesarean section. *Am J Obstet Gynecol* 1987;157:506-510.
29. Keane D, James D. Prophylactic antibiotics at caesarean section do not reduce costs. *Health Trends* 1993;25:84-87.
30. Lynch W, Malek M, Davey P G, Byrne D J, Napier A. Costing wound infection in a Scottish hospital. *PharmacoEconomics* 1992;2:163-170.
31. Rustin F. Sidaway v Bethlehem Royal Hospital Governors and others. *All England Law Reports* 1984;i:1018-1036.
32. Shockett W. Bolam v Friern Hospital Management Committee. *All England Law Reports* 1957;2:118-128.
33. Abdallah A. Gold v Haringey Health Authority *All England Law Reports* 1987;2:888-896.

Examination of witness

DR PETER DAVEY, Reader in Clinical Pharmacology and Consultant in Infectious Diseases, Ninewells Hospital, University of Dundee, was called in and examined.

Chairman

236. Good morning, Dr Davey. First of all, may I thank you for coming along and for providing us with your paper. It would be useful, for the record, if you could just describe who you are and make any opening remarks before we go on to the questions.

(Dr Davey) Thank you. My Lord Chairman, I am a Reader in Clinical Pharmacology at Ninewells Hospital and, also, a Consultant in Infectious Diseases. I wanted to say a few words about what I feel are the most important issues here. Reading the documents submitted by the Royal College of General Practitioners and the British Pharmacological Society, the issue is about the balance, I think, between our desire, as doctors, to make sure that patients with infection receive effective treatment and our duty to the public to not prescribe antibiotics to people who do not need them. These things are easy when you say them quickly but when you start to get down to the detail about defining **need for treatment** it becomes more complex, but I do think we could take a starting point that we would, ideally, like to make sure that patients who will not benefit from antibiotic therapy do not receive antibiotic therapy. We could also say that we would like people who will benefit to receive them. The balance that I think we have to strike is between saying "Our imperative is to make sure that *only* patients who will benefit receive antibiotics" (in which case we would be prepared to put up with some patients who could have benefited not receiving them), and "We are going to see that *all* patients who could

benefit will receive an antibiotic" (in which case we have to put up with some people getting these antibiotics who will not benefit). I feel the balance now is too far in the direction of trying to make sure that all patients who could conceivably benefit get an antibiotic, meaning that lots of people who do not benefit also receive antibiotics. I feel we have got to push the balance back in the other direction. The other point I have tried to bring out is that I feel there is too much emphasis on a conflict of interest between what is good for the individual patient and what is good for the public health and not enough emphasis on the possibility that giving antibiotics to the individual patient is harmful. I increasingly believe that if you give antibiotics to people you damage their normal flora and that leads to problems that we see in things like Candida infection and antibiotic associated colitis in hospital. I think it is important to bring home to the public that **antibiotics are bad for them**. It is bad for the environment but I think we have got to convince the public that their ecology is important, and that giving antibiotics to them is not in their best interests, necessarily.

237. That does lead to the first question of what are the gaps and limitations of the available **information on antibiotic prescription and use** in the United Kingdom in general practice, and how could this be improved? We are aware that you have access to useful information in Tayside. Perhaps you will tell us about that.

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DR PETER DAVEY

[Continued]

[Chairman *Contd*]

A. I think both in the community and in hospitals what we lack is information about patient-specific prescribing. Both in the community and in my hospital, certainly, the only information we get is that a practitioner or a ward used or prescribed a certain amount of antibiotics, but you do not know to whom, of what dose, for how long or any of the crucial things we need to know if we are going to understand the detail. I think patient-specific prescribing is very important. In Tayside we have got around some of the problems by using what is known as a community health index number, which is similar to the NHS number that is now being proposed in England and Wales. In Tayside for the past ten years when you register with a general practitioner you are assigned a number which is your date of birth plus another four digits, which make it unique. That number is then used to index your primary care records but also all your hospital records. I think what Tayside did, which was very far-sighted, was to drive the individual hospitals (or what are now Trusts) to use this number to index all their in-patients records and laboratory records, and it has taken quite a lot of effort to do that. The default is that people always make up a new number. The laboratory will just say "There is this number that everybody else is using but we are going to make up a new one for our records". So you have to really push them and say "No, do not do that", because we want to be able to link information together. The group I work with—the Medicines Monitoring Unit (MEMO for short)—have worked for several years now on linking information about patients together, principally to track adverse drug reactions, but now we are beginning to use this opportunity to look at antibiotic prescribing and resistance. It applies in hospitals too. There are very few hospitals in the United Kingdom who can give you information about individual patients' treatment—never mind what the diagnosis was, or what the indication for antibiotic treatment was.

238. You may have answered this, but who or what mainly influences doctors' prescribing practices?

A. I think the influences are very complex, both in hospital and in primary care. Professor Howie, in Edinburgh, has done some excellent work on this over the last 20 years, showing that there are things that we doctors like to say influence prescribing, such as the patients presenting symptoms and signs, but there is the tremendous importance of context; of where the consultation is taking place, who the patient is, what day of the week it is—if it is Friday evening and you are on call for the weekend your behaviour is going to be different than if it is Monday morning! These are facts, and we may as well acknowledge it. I think context is terribly important. One of your questions was about the pharmaceutical industry. The pharmaceutical industry exploits anxiety. They will use anxiety to say "Well, if you want to be sure use our new, shiny, very broad spectrum drug", and they will talk about vulnerable patients and they will try and get you to use their drugs. That is their business.

Baroness Platt of Writtle

239. Obviously, in the end, the doctor has to use his or her judgment on the question of the individual patient in front of them at the time. Would it be of assistance if there were national notes of guidance in this matter?

A. I think so, and, also, initiatives like **Prodigy**, where there is an inter-active reminder of guidance and evidence, really. I think you have got to remind people at the critical moment when they are making the decision—

240. Whether it is Friday or Monday!

A. I think that will always play a part. I have no problem with that. I am the same. I would prescribe different drugs coming up to a weekend than I would on a Monday, because you know that the staff who are looking after things at the weekend are less experienced. You will make adjustments. I might use a more expensive drug, that is easier and safer for a patient at the weekend, than I would if I was managing the patient through the week.

241. So that is based on judgment?

A. Yes, it is.

Baroness Platt of Writtle] Not just that it is Friday and you are looking forward to going home!

Lord Perry of Walton

242. If you manage to get identification by the use of your number system, how feasible is it to look at all these case notes and get anything that is really sensible out of them? My experience of case notes is that they would not tell you why they chose an antibiotic of one kind or another, it would simply be recorded. Would it not be immensely costly to try and do a survey on that basis?

A. That is an excellent point. We recognise the problem of the case notes and **validation of diagnosis**. It is a key point in epidemiology of all sorts. I think to be able to know which patients received what antibiotics and at what dose would be helpful, particularly in terms of looking at resistance and what drives resistance. That basic information is not there at the moment. I fully support what you are saying but one of the items I sent in my evidence was a very simple sticky label—it used to be a rubber stamp but because they kept claiming it was lost it is now a sticker—which goes in the patient's notes and which makes the doctor record certain basic information. I think Professor Petrie is coming to talk to you in a few weeks' time, but one of the things that SIGN (the Scottish Intercollegiate Guidelines Network) has done on diabetes is to get agreement on what is the standard data set that needs to be recorded on a diabetic every year in order to tell you what their outcomes are. I think we could adopt the same approach: what questions do they need to ask? What clinical signs do they need to record? What laboratory tests, if any, do they need? If everybody was doing that it would be helpful, I think, with something like Prodigy, a standard data set is realistic. Just to say "record these

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DR PETER DAVEY

[Continued]

[Lord Perry of Walton *Contd*]

things" at the time of prescription may give us the information we need.

Lord Rea

243. Could I follow up on that and ask how long your green sticker system has been in operation and whether you have actually been able to use the information for research or service purposes?

A. In our unit, the Infectious Diseases Unit, it has been in operation for a couple of years and, yes, it has been helpful in reviewing, particularly, when to stop antibiotic therapy and, also, changing from intravenous therapy to oral therapy. We have used that. We have been spectacularly unsuccessful in trying to get our colleagues in the general medical receiving ward to use it. We have done two audits and the last was even worse than the first, so we are going to go back again—we are not going to go away—and insist. It really seems to me extraordinary that people prescribe an antibiotic without writing anything in the notes about why they are doing so—but they do.

Baroness Masham of Ilton

244. Very often patients go to a clinic and they find that their notes are not there. Do you think the patients themselves ought to have a sort of passport with their different treatments and their antibiotics written down? They would probably lose them too, but there would be a chance they might not. It would be a cover. Also, do you not find sometimes in hospitals it is the very junior doctors who do the prescribing? I am sure not in your hospital, with you overseeing it, but I have seen many a hospital with very junior doctors doing the prescribing.

A. I think **patients carrying their own records** is an interesting idea.

245. As duplicates?

A. Yes, or, perhaps, some sort of electronic smart card, that carries a certain amount of information. I think we have tremendous opportunities. We have also got problems to solve in relation to **confidentiality** and passing information around electronically, and I think we have to be careful about that. There is, as you probably know, a European law about confidentiality coming into force which I think the United Kingdom needs to look at very critically. We need to get the balance right, again, between confidentiality and the need for good epidemiology. On the **junior doctor** issues, I think that is an extremely important point. Our hospital is no different to any other; the critical decisions get made by inexperienced staff, often in the middle of the night and often under great stress. The consultant will always tell us "Oh, we will review those decisions", but the evidence is that we do not. I am a consultant, and you have to face the fact that you do ward rounds twice a week and you do miss things. One of the things we are looking into at the moment—and this is where I think legal issues are interesting—is what role nurses could have in changing prescribing, because nurses are much more experienced than junior doctors, stay in the same place for longer and, in

principle, we do not see any reason why they could not be the ones to make sure this basic data is collected and perhaps make some of the decisions that relate to that.

Lord Porter of Luddenham

246. Dr Davey, I think you did not have a particularly good word to say about **pharmaceutical salesmen**.

A. They do their job. They sell drugs.

247. I thought you said they oversold.

A. I think they would be delighted to! That is their job. I do not criticise them.

248. Coming to the perhaps more influential and important manufacturer role, do they have a responsibility? We rely on them, of course, for the manufacture of these great things and so on, and they have to sell them, but do they have a responsibility to the public in the matter we are talking about, of over-prescribing and so forth?

A. I am sure they would say that they do. Quite where it is on their list of priorities—

249. Do they fulfil it?

A. I really do not think we can expect the pharmaceutical industry to do this for us. I think we have to come up with the systems for what we think it is reasonable to prescribe.

Lord Dixon-Smith] That is touching on a supplementary that was bubbling up in my mind. Are **doctors being educated, or informed**—because this has to go on throughout their practising lifetime—

Baroness Platt of Writtle] And through their training.

Lord Dixon-Smith

250. - informed of what is happening so that they can make valid judgments rather than be seduced by forceful salesmen?

A. I think that individual prescribers often do lack insight into important pieces of information, and they have to be reminded all the time. I think there is a change of practice going on. I, as an infectious diseases specialist with some responsibilities in general medicine, am absolutely delighted if somebody has written guidelines on how to manage chest pain, or all the other things which are not in my field of interest. I would love clear guidelines about what to do, and I think we are increasingly working that way. The important thing is what Prodigy does, which is to deliver the information at the time of the decision. It needs to be in front of the doctor when they are making the decision. Just going to lectures and so forth does not work very well. We are excited, in Tayside, about the information we are getting about differences in prescribing between training practices and non-training practices. We think that is a reflection of the whole process of being a training practice, that it involves people in thinking through what they do and reviewing what they do. That is, really, what we have got to get people to do.

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DR PETER DAVEY

[Continued]

[Lord Dixon-Smith *Contd*]

251. Is there a difference in the availability of this information between general practice and the hospital service? Is it easier to manage it in hospital services, or do GPs manage more effectively?

A. I think general practices are doing very well and will very soon outstrip the hospitals because their information systems are better. They have already more **electronic information systems**, whereas in our hospital we have extraordinarily bad information about everything. One of my hats is to direct the audit for the Director of Medicine, and I am constantly staggered by how little information we have. If you are asked to look at something like readmissions to hospital and you say to the medical records people "Could you give me a text file, or something I can use in Excel", they cannot. Somebody has keyed information into a computer, it is sitting in a computer and they cannot get it out again, because the system is so ancient and user-unfriendly that we cannot actually access the information.

Lord Perry of Walton

252. We are told that GPs prescribe about ten times as much antibiotic as is used in hospitals, but resistance is undoubtedly more of a problem in hospitals. I presume this is because most of the infections are acquired in **the hospital** where the strains are already resistant, **compared to the community**. If that is right, where should the efforts to influence the use of antibiotics be directed to have most impact?

A. In hospitals we probably do understand things reasonably well, and what determines whether you have an infection with a resistant bug is a combination of who you are and where you are as much as what drug you receive. So, yes, people are vulnerable because they have morbidity and they are vulnerable because they are next to a patient, as you say, who has a resistant organism. However, I think that control of resistance in hospital has a lot to do with infection control and prevention of cross-infection, and probably not quite as much to do with antibiotic prescribing. In the community it is probably the antibiotic prescribing that is really driving this. We have limited evidence for cross-infection of resistant germs in the community. So I think probably the control of antibiotic prescribing as a way of dealing with resistance is more important in the community.

253. But is it not right that the incidence of resistant strains in the community is vastly less than the incidence of resistant strains in the hospital?

A. That is true, but I think it is more driven by the prescribing. You are more likely to see changes in resistance in response to prescribing changes. This has happened in Iceland where they had a problem with penicillin resistant pneumococci and where there was really quite convincing evidence that a change in antibiotic usage led to a change in resistance. That kind of information is awfully difficult to come by in hospital. As I put in one of my tables, because the situation in hospital is so multi-factorial and complex it is difficult to convince people that changing

antibiotic policy changes resistance. That is a much more realistic goal in the community.

254. This is a brutal question, but have we any chance of **winning these battles**, or are we doomed to have an increasing proportion of resistant organisms, both in hospitals and in the community?

A. Not doomed! I think we could improve the balance. We cannot get rid of resistance, and we cannot get rid of infection. There were some extraordinarily naive statements made in the 1960s about the problem of infection being solved. This is a very complex ecological system. What we want is evidence that allows us to look at the balance. In the terms I started with, to what extent are we missing giving people effective treatment when they could get it, and to what extent are we giving treatment to people who will not benefit? I think anyone who has done any audit on prescribing in hospitals or in the community always finds faults of both types. You find people who should be getting treatment who are not, and you find people who should not be getting treatment who are. I think if we keep saying "Let us push that balance in our favour", then we can make progress.

255. So we can make progress in terms of the outcome for individual patients, but can we make progress in reducing in the longer term the incidence of the resistant strains?

A. Iceland is an example where they have done that. In Finland they have done the same with macrolide resistance. Yes, we can.

Baroness Masham of Ilton

256. More and more quite ill people are being treated now in the community. In hospital it is much easier because there are pill rounds to see that they are taking their medication but out in the community—and I am thinking now of people with HIV/AIDS—there are lots and lots of different tablets and sometimes they take them and sometimes they do not. Also with tuberculosis. Is that a problem—just keeping an eye on them? I know with some they have pretty good networks, on the whole, and they ring them up to tell them what they are taking because sometimes of course they forget, as they are ill.

A. I think compliance is an important issue. You mentioned tuberculosis and I think that is an area where it is most obvious this is important and where there is legislation to deal with the problem that if people will not take their pills reliably then we can insist on them being treated.

257. How would you do that? Would you bring them back into hospital?

A. In Scotland we have a Sheriff's Order! I always want to see a sheriff riding over the hill. In extreme cases you can have the patient brought back to the hospital.

Lord Porter of Luddenham

258. You made some disturbing remarks about the **information systems** available to you in hospitals, in particular, if not in general practice. Could I just ask

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DR PETER DAVEY

[Continued]

[Lord Porter of Luddenham Contd]

you to say a word or two about that? What do you think are the faults, and what should we be looking for to rectify them? Is it in the equipment which is provided? Is it in the education of the General Practitioner or of the doctors, or, perhaps, in management?

A. I think information systems in hospitals has been a long-running problem in the NHS. I think it would probably be unwise, on such a complex issue, for me to say anything other than that the problem is still there and there have been a number of initiatives to try and crack this, which have failed.

259. Nobody can do very much about it, unless we have some recommendations.

A. I think probably the single, biggest fault which is still being made is that the information systems are not being designed to provide clinically useful information; they have been designed to provide information on accounting and throughput. When you go to the States in a couple of weeks' time I think it would be well worth asking them about the information they can provide on quality of care, because that is becoming, through the managed care revolution in the States, more and more important.

260. So it is the design of the systems, principally, that you would go for?

A. Yes.

Lord Rea

261. I was wanting to go back to **how to limit the spread of antibiotic resistance** in the community. You say in your summary, 6(d), "The most persuasive evidence would be to show that a reduction in antibiotic practice leads to a decline in antibiotic resistance", and you have briefly mentioned the Icelandic and Finnish experience. That was, particularly, to do with what?

A. The Icelandic experience was to do with penicillin resistant pneumococci being spread around in day care centres. There is a high proportion of children in Reykjavik, Iceland, going to day care centres—a high proportion of working parents—and there was an information campaign aimed at the public and doctors saying that giving antibiotics to children too frequently at day care centres was not a good idea. They did reduce the antibiotic prescribing and they have reduced the transmission of these resistant bugs. The problem in Finland was resistance to macrolide (for example, erythromycin) where a similar approach was taken.

262. Is it just that the resistance of pneumococci to penicillin became lower in Iceland? Or was it the fact that they died out when the antibiotics were not used?

A. I think the use of antibiotic selects out the resistant strains. It allows them to flourish. So if the patient does not receive antibiotics then the normal flora is stronger and better suited. The message that we need to get across is that most of the bacteria that live in our bodies do not do us any harm, and if you eliminate them with antibiotics then you allow the bad guys in.

263. If you saw resistance creeping up, as we have on many fronts seen with certain antibiotics, and prescription of a particular antibiotic was frozen or forbidden for X years, might we then be able to say that it could be a useful antibiotic preserved for use later?

A. That has certainly been done in hospitals. There are good examples where removing an antibiotic from a hospital for a period of time restored its usefulness. It is another reason for optimism, Lord Perry!

264. There is cross-resistance with other antibiotics in many cases.

A. Yes, there is. We have to keep looking. We have to believe we can improve the situation, but I think you have got to make sure you do. You may do something out of good intentions which actually makes the situation worse. That is life.

Lord Perry of Walton

265. Am I not right in saying that there are also well-established cases where stopping the use of the antibiotic does not remove the resistance?

A. Yes. It is complex and there are reasons why that might be so, particularly in hospitals where it is not necessarily the antibiotic that is driving the problem. Nonetheless, I believe we can improve the situation. I think the situation in primary care is we have intense debates about whether children with otitis media should receive antibiotics or people with sore throats. But our work would suggest that the majority of patients who receive antibiotics do not have sore throats or otitis media, they just have runny noses where there is no evidence that they benefit. We should maybe let the people with the sore throats get antibiotics but concentrate on the people who do not have any clinical signs which warrant antibiotics.

Lord Jenkin of Roding

266. Dr Davey has already pointed out what many chairmen of NHS trusts are well aware of, that better information systems would help. I think we would find it helpful if you could spell out how, if you have the better information which you are asking for, this could actually help us in the fight against the resistance problem. If you could do that then I think the priority of putting money into improved information systems might be higher.

A. I think, of the two US guidelines that have been issued, the one by Goldman in the *Journal of the American Medical Association* is more user-friendly because that does outline points of process, of how patients are treated that we need to know about, and points of outcomes that we need to know about. I think they have done a very good job of listing the pieces of information that we need to look at to try and control antibiotic resistance. Whether that will lead to a reduction in resistance I think we would have to say is unproven, but if we were collecting that information and they have identified the critical points of information, you could do trials or experimental interventions to show which of those links we should

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give priority to. I think there is a need for experimental work to tell us what control is most cost-effective, but without the information it is going to be very difficult to run those experiments. I think, if we do not have some of the information electronically we must devise local systems, like our stamp, that allows us to get the information reasonably cheaply.

267. Part of the problem is in the phrase used to us by the Infection Control Nurses Association, that it is very difficult to persuade people to spend money to prevent something happening which would otherwise happen; it is much easier if something is happening to get them to spend money to stop it. I think the essence of the whole approach to this question is the former.

A. I think that is true. With our own trust we are trying to identify areas where they get what they want and we get what we want. One of the areas we are focusing on is intravenous antibiotics, because they are very expensive. They are keen on us controlling the use of these drugs because we will save them money. I think it gives us the information we want as well. If I was going to say to any hospital, what should be top of their list, I think surgical prophylaxis, because it is something which is relatively easy to look at, easy to produce standards, and there are agreed standards on how we should be giving prophylaxis. When you look at it, you find things are not ideal.

268. You make the point that we spend more money on antibiotic treatment on patients who do not have a proven bacterial infection than we do on patients with proven bacterial infections.

A. I think that is true. I think that is what I mean about getting the balance further in the right direction. You have to give antibiotics to some people who do not have infection because that is the only way of making sure that all people who do need treatment get treated. It comes back to the junior doctors. I have no problem with junior doctors, who are inexperienced, starting an antibiotic in the middle of the night, because they think the patient might have an infection. I would much rather they did that and some people received unnecessary treatment than we end up with somebody dying. What we need to do is have a system where that prescription is reviewed the next day and reviewed very critically with criteria for what evidence there is of infection. One has a constant battle. When you say to juniors "We will stop this antibiotic now" they will say to you "Oh, no, we cannot do that; they must finish the course of treatment". You say "Well, they do not have an infection, they do not need to finish the course of treatment". But it takes quite a lot of persuading to stop something once you have started it. I think that is probably where we should be putting most of our attention—trying to stop things sooner.

Baroness Platt of Writtle

269. You talk about your target based approach, which you describe on page 9. The thing that came out of it, as far as I was concerned, is this question of the time between the initiation of therapy and the arrival of the microbiologist's diagnosis. That is, in a way, what you were saying about these junior doctors in

the middle of the night. Is there any possibility that something will be able to be developed so that that junior doctor can go to the end of the ward with a sample and find out what needs to be prescribed before he or she starts?

A. That has been a bit of a holy grail of microbiology for a while—**rapid accurate diagnosis**.

270. It takes two days now.

A. Yes, but it is not just that. The information that you need is not just microbiological but there are other clinical bits of information that we need—chest x-rays, blood tests. Also, identifying other causes for the symptoms that made you think the patient had an infection. So you find that their respiratory symptoms are due to heart failure, not pneumonia. Pneumonia was a perfectly reasonable differential diagnosis, it just happened to be wrong. About 72 hours after the initiation of antibiotic treatment is when you have got the maximum information together and you can also see what has happened to the patient—what has their progress been. Personally, I do not think it is ever going to be easy to make a snap decision "should we start antibiotics now or not"; I think we will always overtreat people, and that is probably right. We have been promised more rapid, accurate diagnostic tests, but I have yet to see them. I think in a lot of the clinical situations, what you have is inflammation and it is very, very difficult to say whether the inflammation is caused by infection or the inflammation happened anyway and that allowed bugs to get in there. Pneumonia in an intensive care unit is a classic example where chicken and egg is very difficult to work out. I really do not think we will ever have a test that says that person has an infection and nothing else. It is just not going to be like that.

Lord Dixon-Smith

271. Surely you get the test which says which infection they have and, therefore, which drug would be appropriate?

A. Yes, but it is going to be very difficult. You will know that bug is there but you will not know whether it is the only thing causing the problem. My microbiology colleagues know that when they do send the result back doctors often say "We are going to carry on with this broad spectrum treatment, just in case". So they are still hard to persuade.

Lord Rea

272. I wanted to ask you about **surgical prophylaxis**. Have any properly controlled studies been done on surgical procedure, which are normally done for prophylaxis, and the outcome measured as to whether it really makes any difference if you give them a prophylactic antibiotic or wait until there is some sign of infection after the operation?

A. There are controlled trials, yes, and I think we need to separate the risk of infection. There are some operations that have a high risk, either in the sense that infection is common after the operation, or that it is very serious, and there are some where both of those apply.

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[Lord Rea Contd]

With colon surgery infection is common, and if you get an infection having had major colon surgery it may kill you, so it qualifies on both grounds. There is good evidence that in colon surgery prophylaxis reduces mortality. So there we have very clear evidence. When you come to something like hernia repair, infection is not particularly common and the evidence there of benefit is relatively weak. At the moment I do not think we have sufficient debate about what level of benefit justifies the use of antibiotics. Cesarean section, I think, is an area of some debate. It is a flagship of the Cochrane collaboration and their evidence based medicine; they always quote this as one of the areas where they did an analysis of several trials and showed that prophylaxis works, that it reduces the infection rate. I think that that is true, but that the risk of infection with modern obstetric techniques in the United Kingdom for elective caesareans is very low. We have a long-running debate with them that we do not think we should give prophylaxis to women having elective caesareans in our hospital because we do not think the risk of infection is high enough. They say that is wrong, and that it is effective treatment that we are denying patients.

Lord Perry of Walton

273. I would like to come in on this statement that **professionals and the public both require education**. We have talked a lot about prevention in hospital, and you have also mentioned that a lot of antibiotic was used quite unnecessarily for runny noses. Doctors say that they are driven by the patient need for a prescription. Would you like to see guidelines published that had some sort of national backing that doctors could use in order to avoid giving prescriptions where the guidelines said "don't"?

A. Yes. There is quite a lot of work going on, I believe, by the Centre for Disease Control in the States in collaboration with some of their colleagues, clinical colleagues, paediatricians and so forth, to develop guidelines for colleagues and information for patients. You need to give the patient some information to go away with which explains the logic of your position and which they can refer back to when they do not quite agree with it. I think that the study by Little from Southampton that was referred to in the British Pharmacological Society statement was very important where they said to patients: "I do not think you need an antibiotic but if you want to get a prescription you can come back any time, you do not have to make another appointment". I think that is a very intelligent way of empowering patients. Most of the people who were given that option did not come and get the antibiotics.

274. Would you include in those guidelines information that you specify in your paper quite seriously about super infections which seem to me, as they seem to you, to be very important?

A. Yes. I think the notion that germs are good for you, that germs are part of your environment, is probably not something that people understand. They have got this vision of women with Dettol bottles

eliminating germs from everywhere and I think we now realise that is wrong, that is not a good thing to do. I am sorry, that is a terribly sexist remark.

Baroness Platt of Writtle

275. Is it not terribly important that that should also be part of the initial training of doctors whether they are going to be in hospitals or GPs? You said lectures do not work very well. Something has got to happen, has it not, so they have got a broader picture of what they should do?

A. Yes. We do try and emphasise this to medical students but it does need constant reinforcement. As we are running out of time I would just like to deal with this legal point because I do think it is very important. As I understand the legal position in the United Kingdom, if a group of experts sits down and writes a policy—for instance let us take the example of caesarian sections, in our Trust we say that based on our review of the evidence we believe that giving prophylaxis to all women is not a good thing to do, it is better to wait for the infection to develop and treat it. Then, of course, eventually a woman will get an infection and may sue us for negligence. My understanding is that if we have made a considered interpretation of the evidence, even if somebody does come to harm it is difficult to sue us. That is certainly not the case in the United States and I think that is one of the things you might like to ask when you are in the United States, to what extent is their practice driven by medico-legal concerns.

Lord Dixon-Smith

276. I think in the light of what we have heard so far, and I understand your recommendations to concentrate on surveillance and particularly of course on the information systems that make good surveillance practicable, is there not also some need for more trials on treatment programmes in infectious diseases in both hospitals and general practice so as to inform and improve the actual use of antibiotics?

A. Yes. I think from your question I got the feeling I had given the impression I was saying only surveillance should be the topic of research. I think I was making a plea for it to be given some priority because it is an area of interest of mine, but I would not like to say that it is exclusively surveillance that we should be doing. Of course we need more **clinical trials** to constantly question the value of treatment. I think it has got to be done on a background of good quality epidemiological information and we have very little information about the link between resistance and outcome actually. It is a little hobbyhorse of mine and I did not put it in here because I would go on at length about it. I think there are some examples of quite simple infections like cystitis where we know that Trimethoprim resistance is increasing, we know that about 30 per cent of the bacteria that cause cystitis are resistant to Trimethoprim in Tayside, but what does each percentage increase of resistance do to the chance of the woman recovering if she receives Trimethoprim? I do not know the answer to that. There

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are situations where Trimethoprim resistance might lead you to use another drug which is actually inferior to Trimethoprim. A final point is are we going to direct our treatment at the 30 per cent of patients who have resistant bacteria or at the 70 per cent of patients who have sensitive bacteria, who gets the priority?

Baroness Platt of Writtle

277. What do you feel about the use of antibiotics in animal husbandry?

A. I had hoped we had run out of time! I would rather they did not, I suppose, but I do not think that is a very informed judgment. Chairman

278. One point we did not deal with in detail is what you might suggest we ask when we go to the USA

A. I will write to you a little note.

Chairman] Thank you very much for coming along.

Supplementary letter by Dr Peter Davey

A few additional thoughts following the hearing:

I have been thinking about Lord Perry's question about why we should pay attention to resistance in the community, when most of the problems occur in hospital. On reflection I think that possibly the most important reason is that the bacteria which cause infections in the community are more contagious and more virulent than the bacteria which cause infections in hospital. That may sound paradoxical, but in order to cause community acquired infection an organism has to be capable of infecting people who are otherwise healthy, whereas in hospitals less virulent bacteria are able to prey on weaker hosts. If one of the people in the room on Tuesday was carrying a drug resistant enterococcus I doubt that anyone else would have come to any harm, whereas if they were carrying drug resistant pneumococcus that may not have been the case.

The editorial which I gave to you after the hearing¹ contains some very interesting looking references about patient expectations and patient information. In particular, I think it would be very important during your visit to the USA to obtain copies of reference 22: *Your Child and Antibiotics: Unnecessary Antibiotics Can be Harmful* published by the Centre for Disease Control in 1997.

An additional paper which has just come to my attention² illustrates very nicely the issues of sensitivity and specificity which I raised during the committee. The study, done in Egypt, tested the criteria recommended by the WHO for diagnosis of streptococcal sore throat in 451 children. The WHO only recommend antibiotic treatment for patients with *both* exudate on the pharynx *and* enlargement of lymph glands in the neck, but the study also looked at what would have happened if the rules were relaxed so that treatment would occur if either sign was present. The results are strikingly different:

	Both signs present	Either sign present
<i>Sensitivity</i>	13/107	90/107
Number (per cent) of patients with +ve cultures who would have received antibiotics	(13 per cent)	(84 per cent)
<i>Specificity</i>	323/344	138/344
Number (per cent) of patients with -ve cultures who would <i>not</i> have received antibiotics	(94 per cent)	(40 per cent)

Unfortunately there is a weakness to the design of this study which is discussed in an accompanying editorial.³ This is that children with positive throat cultures may have been carrying streptococcus in their throats and have coincidentally had a viral throat infection; culture of the streptococcus is not proof that it caused the symptoms. An additional test of immune response to infection would have made the study more rigorous.

Nonetheless, I think this is a good example of the type of epidemiological study which we need in order to inform the debate about the consequences of applying simple decision rules to guide antibiotic therapy.

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¹ Schwartz, B., Bell, DM and Hughes, JM Preventing the emergence of antimicrobial resistance. A call for action by clinicians, public health officials and patients. *JAMA* 278:944-945, 1997

² Steinhoff, MC El Khalek, MKA, Khallaf, N Hamza, HS, El Ayadi, A, Orabi, A, Fouad, H, and Kamel, M. Effectiveness of clinical guidelines for the presumptive treatment of streptococcal pharyngitis in Egyptian children, *Lancet* 350:918-921, 1997.

³ Kaplan, EL Clinical guidelines for group A streptococcal throat infections. *Lancet* 350:899-900, 1997

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Memorandum by the Royal College of General Practitioners

1. *Infectious diseases in general practice*

1.1 Illnesses which are presumed to be caused by infective organisms are a major part of the work of general practice. In addition to well known bacterial and viral agents there has been increasing awareness of more recently identified agents such as campylobacter/helicobacter, chlamydia and mycoplasma, all of which are susceptible to antibiotic therapy. There is also increasing recognition of the long-term and potentially serious effects of these apparently minor infections, with the possibility that other long-term effects of minor infections remain unidentified.

1.2 Diagnostic Uncertainty. In general, there are no clinical features which will reliably identify the diagnosis or underlying organism at an aetiological level. Therefore, although doctors are aware of the range of organisms which commonly cause a given syndrome, such as sore throat, otitis media or bronchitis, it is not possible in any individual case to identify the organism likely to be responsible on clinical grounds alone with any great degree of accuracy. Although antibiotics will not be effective in viral illnesses it is not usually possible to distinguish viral from bacterial infection on purely clinical grounds. Most infective syndromes may be caused by both viruses and bacteria in varying proportions. For example the ratio of viral to bacterial causes may be about 40:60 in the case of sore throat, as against 80:20 in the case of otitis media. The higher the ratio, the more likely it is that antibiotic therapy might be effective in an individual case.

1.3 Threshold for medical consultation. Many people do not seek medical advice for these common infectious diseases and most will recover without medically prescribed treatment. There is widespread variation in the threshold at which individuals decide that medical advice is required. The fact that not all individuals seek treatment is, however, not an argument that none should do so. There is insufficient evidence to recommend that antibacterial treatments should not be used for apparently self limiting infections.

2. *Antibiotic therapy: The balance of efforts*

2.1 Our search of recent literature has not altered our view that, in general, given the context of diagnostic uncertainty, current prescribing practice of general practitioners is in general more beneficial than harmful in the care of individual patients. There is, however, a potential conflict between individual and public health interests.

2.2 We do not feel qualified to comment on the extent of the effect that widespread medical use of antibiotics has on the development of resistant organisms, but accept that there must be an effect. It is generally agreed, therefore, that there should be limitations on the medical use of antibiotics.

3. *Limitations on Medical Use of Antibiotics*

3.1 Licensed antibiotics are, by definition, of proven effect against specified bacterial infections even where these infections (e.g., bacterial respiratory infections) might be self limiting. The main issue is, given a general acceptance that use of antibiotics should be limited, mainly for public health reasons, at what level (if any) should they be withheld in individual cases even although there might be a reasonable expectation of benefit. The difficulties of diagnosis have already been described. These difficulties in deciding whether or not antibiotic use might on balance be beneficial in an individual case are compounded by the fact that early institution of antibiotic therapy might be important where apparently minor illnesses prove to be due to serious infection (e.g., acute pyelonephritis, pneumonia). Early decisions have therefore to be made on the basis of minimal evidence.

3.2 In theory, there are a number of levels at which the beneficial effects of antibiotics might be withheld. Antibiotics might be reserved only for:

- (i) life threatening infections;
- (ii) (i) plus infections that might have important sequelae, e.g., lasting damage to body systems such as the lungs, kidneys or ears;
- (iii) (i) and (ii) plus symptomatic benefit, e.g., reduction of severity or duration of symptoms, where there are implications for individual wellbeing and for the national economy.

There would be general acceptance of antibiotic use at levels (i) and (ii), but it would not currently be possible to withhold antibiotic use accurately to this level, for reasons that have been outlined earlier. There would inevitably be some "overspill", due to unavoidable inaccuracies in diagnosis and proper caution (so that "serious" diagnoses were not missed).

Any controversy about medical use of antibiotics relates more to the purely symptomatic level (iii), especially where that can be clearly defined in clinical terms (e.g., sore throat, bronchitis and asthma, acute otitis media, lower urinary tract infection). These are thought to be largely self limiting illnesses, although it is possible that

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there might be so far unidentified long-term effects. Some important long-term effects of apparently minor infections have only recently been identified (e.g., campylobacter) although others (e.g., streptococcal sequelae) have been known for some time. There might therefore be unknown beneficial effects of antibiotic use for apparently self limiting infections.

3.3 Given that these syndromes (e.g., sore throat) are extremely common and that aetiological diagnosis is inevitably highly inaccurate, how justifiable is the widespread prescribing of antibiotics for such illnesses if (as seems likely) there is on balance a marginal benefit for a large number of individuals? It seems likely in the case of sore throat for example that a liberal prescribing policy might result in reduction in the duration of symptoms by one to two days in perhaps 50 per cent of people, plus reduction in the severity of symptoms in the same number. Of course, over the country as a whole this would be a large number of people and there would be various knock-on economic effects.¹

3.4 Whether or not and how far antibiotic use for relief of symptoms of self limiting illness should be limited should not be a matter for doctors to decide, but the subject of public policy. In a context in which antibiotics are much more freely used in agriculture and food production it seems unlikely that there would be much public support for such restriction.

It is likely that doctors follow rather than lead public opinion in these matters and for so long as patients expect treatment for these illnesses, doctors will provide it, although it is well established that doctors may overestimate the patient's expectation of a prescription.² Public policy would need to take account of increasing "globalisation". Antibiotic use in UK is already lower than in many other European countries. In that context it would be difficult to operate a more restrictive policy.

3.5 In our view, therefore, general practitioners need to operate within a framework of public consensus. Their main role is to act as personal medical advisers and advocates for individual patients. Where there is a public expectation that certain treatments, such as antibiotics, will be provided, it is difficult for the general practitioner to withhold treatment for public health reasons whilst preserving a good doctor-patient relationship. Whilst it is certainly a function of the general practitioner to educate patients to make better use of health care, there is potential for conflicts of interest if the doctor is both advocate for the individual and guardian of the public interest.

3.6 Nonetheless, there is sufficient evidence of widespread variation in the utilisation of antibiotics to suggest that there is scope for further reduction of their use by some practitioners. There is no shortage of guidance on the use of antibiotics (e.g., British National Formulary (BNF) and local formularies) but there may be problems of implementation. It seems likely that further development of electronic decision support systems (such as Prescribing Rationally with Decision Support In General Practice Study (PRODIGY), sponsored by the National Health Service Executive) will be a major aid to implementation.

3.7 We also recognise that poor compliance with prescribed antibiotic regimes may be a factor in the production of resistant organisms. Compliance is likely to be greater where the substance prescribed is easier to take (e.g., because of fewer adverse effects, longer dosing intervals or shorter courses) and greater attention might be paid to this, even where the preferred preparation is more expensive. We also support better provision of written information and instructions to patients in line with recent EU legislation and we support the recent initiatives of the Royal Pharmaceutical Society of Great Britain (RPSGB) in respect of compliance/concordance.

3.8 Lastly, there is also a need to consider qualitative limitation on antibiotic use, that is the differential restriction of use of certain classes of antibiotic. For example, it may be prudent to minimise the use of new classes of antibiotic and to avoid unnecessary use of wide as opposed to narrower spectrum antibiotics, in order to limit the emergence of resistant organisms.

We do not propose to discuss this in detail as it is more properly the province of microbiologists who advise Health Authorities (HA's) on the range of bacterial sensitivity and resistance in the local area. Most HA's issue recommendations based on this guidance. We entirely agree with the need to have local rather than national recommendations in this particular instance as there may be considerable regional variation in these results. Many areas have local formularies based on these results. There should be general practitioner input in the selection of antibiotics to be used.

4. *The prospect of "over-the-counter" (OTC) antibiotics*

4.1 In recent years the Medicines Control Agency (MCA) has operated a specific programme of deregulation of medicines from Prescription Only (POM) to Pharmacy (P) and from P to General Sales List (GSL).

4.2 We are in favour of providing consumers with wider access to a range of more modern medicines than was hitherto available but, in general, we have concerns about some aspects of the implementation of this policy. In many cases (as would be the case with antibiotics) these newly deregulated medicines remain prescribable under the NHS and are considered to be possible "necessary treatment" under the provisions of the NHS contract for general practitioners. In the present context our main concern would be that an inequitable situation might

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be created whereby patients who could afford to do so could buy antibiotics directly from a pharmacist whereas poorer patients might still have to consult a doctor in order to obtain a "free" prescription. We have discussed elsewhere how this inequity might be resolved.³

4.3 In principle, where the MCA considers it safe to do so, we would not object to the direct sale of certain antibiotics. Such a move, however, might run counter to the efforts of the profession and others to curtail the use of antibiotics. If there is excessive use under the medical supervision, this is likely to be greater if supervision is relaxed. Delegation of supervision to a pharmacist ((P) category) would not necessarily improve control as pharmacists are subject to the same problems which we have already outlined for general practitioners. Pharmacists are also subject to a potential conflict of interest in that refusal to sell the medicine generates no payment. There is little or no evidence to suggest that pharmacists regularly refuse to sell medicines to clients: in most cases the medicine is sold on request.

4.4 Consideration of deregulation of antibiotics would be better undertaken within the framework of some new national consensus on how far these substances would be used for symptomatic relief in apparently self limiting illness (see paragraph 3.3). Within such a framework it would be easier to identify which (if any) agents should be released.

4.5 Finally, the development of reliable instantaneous diagnostic testing (e.g., for streptococcal throat infections, urinary tract infection, etc) might encourage the deregulation of antibiotics. If there is a reliable diagnostic test, the need for medical advice or supervision is mostly redundant in these particular examples.

References

1. Little PS and Williamson I (1994) Are antibiotics appropriate for sore throats? Costs outweigh the benefits, *British Medical Journal*, 309; 1010-2.
2. Cockburn J and Pit S (1997) Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations—a questionnaire study. *British Medical Journal*, 315; 520-523.
3. College evidence to Medicines Review Team 1997.

Dr Bill Reith FRCP Edin FRCGP

Honorary Secretary of Council

Royal College of General Practitioners

Examination of witnesses

DR ROSS TAYLOR, Senior College Member, and DR SCOTT BROWN, Vice Chairman, College Council, the Royal College of General Practitioners, were called in and examined.

Chairman

279. Perhaps you would like to introduce yourselves and make any opening comments before we start the questions?

(Dr Brown) My name is Scott Brown. I am a general practitioner. I practise in Coleraine in Northern Ireland. Northern Ireland forms one of the faculties of the Royal College of General Practitioners, of which there are 32. My role on the Council is as the faculty representative for Northern Ireland and also Vice Chairman of the College Council in London.

(Dr Taylor) I am Ross Taylor. I am a general practitioner in Aberdeen and a senior lecturer in the Department of General Practice there. I have a long standing interest in prescribing medicines and the research into it and I am Chairman of the Prescribing Advisory Group of the Royal College of General Practitioners.

280. You say in your documentation that "it is generally agreed...that there should be **limitations on the medical use of antibiotics**". In the context of

general practice, what form should this take? If the GP cannot act as a "rationer of resources" in the interest of public health then who can?

(Dr Brown) I think, my Lord Chairman, this goes right to the heart of one of the problems faced by most general practitioners and that is the attempt to marry the role as patient's advocate with awareness of one's responsibilities at a national level. I think there is certainly a very strong case for general practitioners having a strategic role and having input at a strategic level. We have heard from Dr Davey already about some of the discussions about guidelines and prescribing recommendations and we certainly would support those. The difficulty is obviously at an individual level. I think our College would be keen that while we would wish to provide whatever evidence necessary, and we would be firmly of the opinion that there are views that we would want to take, our principal responsibility to our patients would preclude us from wanting to be heavily involved in any sort of political, with a small 'p', or overtly financial, with a

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DR ROSS TAYLOR and DR SCOTT BROWN

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small 'f', role in the doctor/patient relationship. Having said that, the College believes that there are precedents for the modification of our patients' behaviour in relation to pharmaceutical preparations which have been deemed undesirable, or where the risks of continuing usage have deemed them as less than satisfactory for patients. I am referring specifically to barbiturate and amphetamine usage. If this Committee would like a more specific example in relation to the topic this morning, a specific antibiotic, namely Co-Trimoxazole, has now largely been removed from the therapeutic armoury of most general practitioners. These changes have come about as a result of a national initiative which is an input from a number of bodies, including the profession, and that has translated itself into a change in prescribing activity in general practice.

Lord Perry of Walton

281. The problem area of antibiotic prescribing in general practice is the area of symptomatic benefit in self-limiting diseases, where there is no danger or very little danger of death or serious lasting ill-effects. You say that this is a matter for public policy rather than for individual GPs and you call for a "new national consensus". What would you like that consensus to be, and how would you like to see it achieved? Ought it to take account of the other point I raised with Dr Davey, namely that the risk of super infection has got to be part of the guidelines?

(*Dr Taylor*) If I might preface this one by saying our view would be that the use of medicines generally is something that varies between countries. The way we use medicines in Britain is different from the way that the Germans use medicines or the Americans use medicines. That is what we are talking about, we are talking about some sort of cultural framework within which we work. In fact, the cultural framework for the use of medicines in this country is quite conservative, or has been up until now, in comparison with other countries against pressure from the pharmaceutical industry, particularly the American based pharmaceutical companies, and to some extent against pressure from consumer interests. As I say, I think our view is that doctors work within that framework and it is very difficult to work outside it. It is very difficult, if the general culture is the use of antibiotics for minor respiratory disease, to be one of the doctors who says "no, my patients cannot have that treatment", because for one thing your patients just go up the road to the next doctor who does. So all the time we are working within that framework. I think it is possible to change the framework and as Dr Brown said that happened with drugs like barbiturates and amphetamines and benzodiazepenes to some extent. An important part of it is that there is a public agreement that the public will not demand these drugs. First of all there is a lack of evidence across the board on the use of antibiotics and the use of antibiotics for these kinds of illness. If there was a general view, generally agreed view, based on the evidence that on balance for the public health interest it would be best to limit the use of antibiotics for these illnesses, even though there might be some

benefit, and that is an important point to make, if there was that kind of public consensus then it could be implemented in the way that these previous voluntary bans were implemented, partly through a campaign of public education and partly through education of doctors, but mainly the doctors ourselves would have the support of a public consensus in implementing it with our patients.

Lord Porter of Luddenham

282. Do you feel that **over-promotion of antibiotics** by salesmen and manufacturers is contributing to the problem we are talking about, or is it perhaps a necessary part of the job of the manufacturers who have to produce these things?

(*Dr Brown*) I think many of our colleagues would view it as a necessary consequence of the promotion of a new development. It would be an unusual general practitioner who would accept what a pharmaceutical representative tells him or her as being the gospel truth and most would wish to seek at least one alternative opinion. Nevertheless, it does provide information for many GPs about new developments. The amount of paperwork in general practice and the workload in general practice is outwith the remit of this Committee but nevertheless it contributes to one of the problems about keeping up to date with new developments in antibiotics. Having said that, there are many of our colleagues who do not see pharmaceutical representatives. My opinion, certainly within Northern Ireland where I am a GP tutor, is that more and more practices are in fact not opening their doors to pharmaceutical representatives, they are choosing to obtain their information from different and possibly more objective sources. Nevertheless I think the College opinion would be that it is a necessary function and it is one that is useful for most of our members.

283. Unless the manufacturers do have some indirect support in this way we are not going to get new antibiotics?

(*Dr Brown*) That is correct.

(*Dr Taylor*) Could I add to that? I think the fundamental problem is that in this country medicines are licensed on the basis of effectiveness, not comparative effectiveness. So if an antibiotic is licensed a company can quite legitimately—and in fact has an obligation to its shareholders—promote that medicine for its effect in the disease that it has been shown to have that effect, whether or not there is another antibiotic already available that might be better. There is a problem with comparative efficacy. If there was the sort of national consensus that we referred to earlier then of course the pharmaceutical industry would have to work within that consensus. I think we recognise the point that has already been made, that there is also a conflict of interest for Government in the promotion of a healthy pharmaceutical industry, one of the most successful industries we have, and the protection of cost-effectiveness of the health service.

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[Continued]

Chairman

284. At the individual practice level who would be the person who would most likely meet and discuss and negotiate with the salesman? Would it be the principal of the practice or would it be the practice nurse?

(*Dr Brown*) It would usually be the practice manager or the senior receptionist, whoever was acting in the senior managerial role, and that person would allocate slots within different surgeries or at the beginning or the end of surgeries for pharmaceutical representatives. I would have to say that most representatives are extremely sensitive to the needs of patients in the surgery and are very flexible and very understanding about attending and waiting to see GPs. That would be the usual method and manner in which they would get access to the GPs.

285. So essentially it is someone in the practice who knows the requirements of the practice?

(*Dr Brown*) Yes. Some of these appointments are booked up six, 12 months in advance. This is not an unusual occurrence. If a practice, like my own practice, takes a decision that we will see so many representatives during certain surgeries and at certain busy times, (for example, on Monday we do not see representatives because patient workload is excessive) then what happens is that these slots become booked and representatives, in fact, end up booking six to 12 months in advance.

Lord Rea

286. Particularly with regard to antibiotics, which is the topic of our enquiry, is not one of the problems that drug representatives offer a new antibiotic which might have marginal advantages, like less side effects but also a broader spectrum, and encourage the GP to use that as a first line drug when in fact it would be much better to be kept in reserve for when the normally used cheaper and perfectly effective drug is ineffective?

(*Dr Brown*) I think that is a risk. It is not my usual experience to meet a representative who is marketing a new drug, allegedly more effective, slightly broader spectrum, which is cheaper than the existing drug.

287. No, no, they will be more expensive. Price is not what I am trying to emphasise. This is a second line drug which should be held in reserve but which is promoted as an effective first line drug in case you should have a resistant organism.

(*Dr Brown*) I made reference to the cost merely to make the point that most reasonable general practitioners would continue to prescribe the cheaper clinically effective alternative but there is an intellectually attractive argument when a representative makes that very point, namely that "this is something which is more expensive but we believe it is more effective, and we are suggesting you hold it as a second line should what you are prescribing at this stage not work for your patient". I am sure there is some psychology that the

pharmaceutical companies have examined very closely and I am sure they believe that this is a way of effecting change with general practitioners and their prescribing policy.

288. My experience is that sometimes second line antibiotics tend to get used too much as the first line.

(*Dr Brown*) I am sure that is the psychology of the pharmaceutical companies, that if they leave it there and leave the apparent decision to the general practitioner, tantalisingly dangling something which is more effective, then there is an incentive to perhaps prescribe that. The other thing very often that happens now with the new preparation is that in fact not only is it marketed as being more effective but there is more likely to be better compliance because the courses are often of a shorter duration and taken less frequently in a given day and that is an attraction for GPs and for patients.

Baroness Platt of Writtle

289. You say: "Early prescribing decisions...have to be made on the basis of minimal evidence" and you look forward to the development of reliable **instantaneous diagnostic testing**. How far off is this prospect? Then will you tell us something about **PRODIGY** in your paragraph 3.6?

(*Dr Taylor*) We would have to mostly give you further written evidence on that. As Dr Davey said, we know there are problems with instant diagnostic testing so I cannot honestly say how far off it is. We actually do have a working party in the College that is dealing with this. We have not had time to consult with them. We may be able to submit some further evidence on that.

290. It may be getting quicker rather than instantaneous.

(*Dr Taylor*) Anything would be better than nothing I suppose is one of the answers to that. Moving on to **PRODIGY**, again I think we could give your Clerk details of how to obtain more complete information about that than I could give you here. Fundamentally this is a way of providing general practitioners with instant guideline based information on the screens of their computers where now most general practitioners in the country as a whole—it is difficult to estimate exactly but at least three-quarters—would have computer terminals on their desks in their consulting rooms. This is a way of providing expert guidance instantaneously to them whilst they are actually dealing with the patients. The system can present a series of algorithms which will help the choice of antibiotics. It would be a very good way of implementing the sort of consensus and national guidance that I mentioned earlier.

291. How far off being able to be put on everybody's screen is that system?

(*Dr Taylor*) That system is available now.

292. It is there now, but presumably it costs money. It is being sold, is it?

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[Continued]

[Baroness Platt of Writtle *Contd*]

(Dr Taylor) It is an experimental system which is being sponsored mainly by the Department of Health.

Lord Rea

293. What percentage of GPs have got access to the PRODIGY system?

(Dr Taylor) Because it is an experimental system it is limited to those who are participating in the experiment. We think it is just over 200 practices. I should say that there are other systems as well being developed, it is not the only system but it is the system that is being tested by the Department of Health.

Baroness Masham of Ilton

294. If there are complicated infections can the GPs speak to the hospitals and do the computers talk to each other? When I was on the FHSA this was a big problem, the hospital computers did not talk to the GP computers and there was definitely a lack of communication between the two.

(Dr Taylor) I think that is still the case. I am not quite sure what circumstances you would be referring to. There might be in the future, and there are already, systems which allow transfer of information from hospital laboratories, say, to general practice which would speed up the problem that was mentioned earlier of getting back test results. It still does not make it fast enough but at least it cuts out the post. These systems are already available.

295. In one of our local hospitals in Yorkshire just recently there was a case of a patient coming from the community into hospital with E.coli and two people died and several people were very ill. Perhaps if there had been better communication that could have been stopped.

(Dr Taylor) Certainly, although that does not seem to me to be necessarily a matter to do with computers, it is about information.

296. Information.

(Dr Brown) There have been developments over the last few years on laboratory links between practices and labs and some systems have worked better than others but those are being continuously redeveloped and modified. I think one of the problems with the PRODIGY package and the other packages that Dr Taylor has referred to is the difficulty of matching software with the several different types of software available in general practice throughout the United Kingdom. There has been some consolidation among computer companies but there are still several main players out there and there is a move now towards Windows based systems and the likelihood is that the operating system for the software packages will become standardised. I think when that happens, as with most developments in PCs and computers, there will be a sudden increase in the amount of data immediately

available to GPs and that will be a very exciting situation.

Baroness McFarlane of Llandaff

297. You have already talked about the climate of opinion about antibiotics in which you are working but you say in your evidence: "So long as patients expect treatment...doctors will provide it." How would you characterise **public attitudes to antibiotics** in the United Kingdom? Are they right, and are they changing? You also say: "It is well established that doctors may overestimate the patient's expectation of a prescription". Could you explain that to us, please?

(Dr Taylor) We actually did try to find some evidence on the first point. There is very little evidence about change in public attitude. What we know certainly is that consultation for these minor infections, respiratory illnesses, is still a very high proportion of the work of general practitioners, particularly for children. It is not clear exactly how that may have changed over the years. Certainly it would be one of the things in the research agenda that we mentioned. There might also be socio-economic differences in the attitudes of people towards how they deal with these illnesses and we do not know much about that either. It is possible incidentally to get data on consultation rates and morbidity in general practice which again we could give you details of. The second point is more substantiated because there have been a number of studies over the years which seem to show that if you ask patients before they go into the general practitioner's consulting rooms what their expectations of wanting a prescription and getting a prescription is and then if you subsequently ask doctors what their expectations of the patient's wishes are, there is quite a big discrepancy and the discrepancy is normally in the direction of the doctor. Doctors tend to overestimate the patient's desire for a prescription. That is interpreted usually as meaning that a lot of patients simply want reassurance and do not necessarily need a prescription.

298. There is a lot of public education, is there not, in journals and the press? I wondered if this was something that we ought to press for more, that there is a broader perception on the part of the public?

(Dr Brown) The difficulty is marrying up the public information on health promotion, early diagnosis, early attendance at your primary care physician, with a similar very valid message that some of the symptoms that you are experiencing as a patient are minor, are self-limiting, and if you allow two or three days they will resolve and settle. There is a huge need for education of the public. Despite what we have said in our submission about the apparent evidence, there is still a huge demand from patients. Coming from the coalface as we do, as practising GPs, it is usually a fairly persuasive argument that is needed to reassure a patient that

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[Continued]

[Baroness McFarlane of Llandaff Contd]

they do not necessarily need an antibiotic. It also has major workload implications as well. It is one thing to say to the patient "I believe this is a viral infection but I will see you in two days, I will give you an appointment in two days, please come along and at that stage I will prescribe an antibiotic", but that has major workload implications for most GPs. It is easier when you look at the logistics to say "It may be, it may be not, we will give you this anyway" and that then feeds into the loop and the next time the symptoms recur the expectation of the patient is that bit higher. I think education is required both of the general practitioners prescribing and also of the patients.

Baroness Platt of Writtle

299. It seems to me that in families it is nearly always the mother who is going to make sure that the pills are taken and is going to take the child to the doctor, and you said it is children who have very often these large numbers of minor complaints, and a great many women read women's magazines. As a scientist I am perfectly prepared to read a scientific document but for most women a really jolly article in a women's magazine telling them about the fact that germs are not the enemies, they are in fact the friends, might make a big difference. There is a big spread of women's magazines. I wonder if anyone is making efforts in that direction?

(Dr Brown) That goes back to some of the research proposed we have later. We fully endorse what you are saying. The method of getting the message to patients has got to be diverse and widespread. The difficulty is that very often the sorts of patients who consult and who, if you like, come immediately and who demand an antibiotic are the types of mothers who come from backgrounds where there are social problems and there is an inability perhaps to lift *Cosmopolitan* or another magazine and read that.

300. But they might read *Woman's Own* or *Woman's Weekly*?

(Dr Brown) They may do, or they may have the television going and they may listen to a television doctor.

301. Yes.

(Dr Brown) These are all areas which need to be explored. We would certainly support that sort of initiative.

(Dr Taylor) The College does actually produce some educational information for patients.

302. I was just wondering whether you go into the field of magazines because I think that might be rather a user friendly way of getting over this sort of thing?

(Dr Brown) We have a press unit which is frequently asked for opinions and many of our officers do contribute to that. When you consider the number of publications available on a monthly and even a weekly basis it would need several officers working full-time available 24 hours a day

for the press and media to get the information that they require. There is an insatiable appetite for health matters and health issues but nevertheless we have to look at it.

Baroness Masham of Ilton

303. Some patients have a lot of pressure on them if they are working. On the other hand patients have demanded appointments systems. I live in a rural area and to get an appointment now it is really very difficult and then you get three minutes. If you are working and you have got a long way to go you just have not got time. It is quicker for the doctor and the patient just to give him an antibiotic. There is a lot of pressure on some patients, pressure of work.

(Dr Brown) I agree. Pressure on patients and pressure on the practitioners as well. One of the innovations which is starting to occur in a number of practices on a research basis is the use of community pharmacists in practices actually looking at repeat prescribing and prescribing over the telephone where this very scenario is worked through. I think that will provide interesting and exciting information about how best to both **prescribe effectively** and at the same time reassure those patients who for very understandable reasons cannot get an appointment when they immediately want to.

(Dr Taylor) A very useful strategy, which was mentioned earlier, which more and more of us I think are doing and has been done for quite a considerable time is to give patients a prescription for antibiotics but to say "You need not use them immediately. Wait for a day or two", particularly if it is a weekend, "if things are getting worse take the prescription" and the result of that is that many patients do not in fact take the prescription.

Lord Dixon-Smith

304. In paragraph 3.7 you discuss the question of compliance, or is it non-compliance, with prescription regimes by patients. You mentioned that there has been some European Union legislation on the instruction or **information for patients** and also an initiative by the Royal Pharmaceutical Society. Could you just discuss those a little bit further and also whether there are other international aspects to this whole spectrum that we ought to hear about?

(Dr Taylor) I could preface my remarks again by saying that you will be able to obtain more comprehensive and accurate information directly from the Department of Health on the EU legislation question. We will give you a copy of the Royal Pharmaceutical Society document. In summary, as I understand it, the EC legislation requires that every medicine that is dispensed will contain a leaflet according to a prescribed form which is for the patient's use. So every dispensed medicine must contain a patient information leaflet. The way that initially the United Kingdom chose to handle that was by having pre-prepared standardised patient packs which would contain these leaflets, so that

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[Continued]

[Lord Dixon-Smith *Contd*]

instead of the pharmacist taking a number of tablets out of a bottle from stock, he would simply take down a pack of standardised size. At the moment I believe that way of handling the need to comply with the EU legislation may be being reviewed because there are additional costs involved in having these standardised packs. On the second question, there has been a recent report from the Royal Pharmaceutical Society on the importance of compliance. I think the best way of handling that is simply to supply you with a copy of the report, which we will do.

Lord Jenkin of Roding

305. We had some pretty powerful evidence a few weeks ago from microbiologists that in countries where antibiotics are freely available **over-the-counter** the problem of resistance is a great deal more pressing than it is here and, therefore, I was very surprised to read in your paper that you would not object to such a development "in principle". I wonder whether you would like to explain that?

(*Dr Taylor*) It certainly does require some explanation. It is because it is really an extremely complex issue, as I am sure you appreciate. What we have said initially is we have no doubt that if antibiotics were made available over-the-counter through pharmacies there would be an increase in the use of these antibiotics. It is not for us to say, in a sense, that that should not happen because there are important considerations in both directions to be weighed up. There are consumer pressures to allow patients to have greater access to drugs directly, as they do in other countries. There are trade pressures, pharmaceutical industry pressures, to do this perhaps as well. These have to be balanced against the downside which is the spread, or possible spread, of resistance, possible public health disadvantages of the use of antibiotics. Someone has to weigh these issues up. What we are saying is we do not feel that it is our place to do that, it is a political decision in a sense. If the MCA, which is the body concerned, considers this and makes the decision that some antibiotics might be made available then I think we would have to go along with it.

306. That is a very different thing from saying that you would not object in principle. I would have thought that the medical profession, particularly those who are concerned with this increasing problem of resistance, would be the people who would say "This is a major national public health issue, anything which is going to make it more difficult to combat resistance we as doctors would oppose". In a sense I get the impression that you are selling the pass on this. I accept that it is a decision for the MCA but I would have expected the profession, as have many professional witnesses who have appeared before us, to take a very strong line and say that this would clearly be a step in the wrong direction.

(*Dr Taylor*) I think what we are saying is that if the MCA asks for advice on this, which it would,

that is the advice we would give, that we do not think it is a good idea. But if the conclusion that they reached at the end of the day was that some compromise would have to be made, we would have to go along with that.

307. I think that is a very important gloss on your written evidence. I am glad we have got it on the record. I am sure we will take note of that.

(*Dr Brown*) We would be grateful if you would.

Lord Porter of Luddenham

308. Who funds the research for any projects the RCGP would like to see done? You are not like a hospital or a medical research council. Is there a research body in your College which organises this?

(*Dr Brown*) There are a number of sources that we could access for funding. Certainly within our own College we have the Scientific Foundation Board with very limited resources and that, in fact, is funding some research at the moment and Dr Taylor can advise you on that. The major source of potential funding since the Culyer Report has been published is now the Regional Director of R&D. The method by which general practice and general practitioners can apply for funding has changed quite dramatically. There is quite a lot of work being done now to explain to interested general practitioners and primary care professionals how to make application for that funding. Our concern would be that most of the funding would be directed towards secondary and tertiary care research. As you would expect we would want to make the case for primary care. That would be the single most significant source of funding.

Baroness Masham of Ilton

309. I live in an area where a pocket of leukaemia exists. Our GPs certainly were doing research with Leeds University, I am not sure if they are still doing it, and in fact one of the GPs himself died of leukaemia. How much contact with universities and research is there?

(*Dr Brown*) There is quite a considerable amount. Dr Taylor, as well as being an NHS GP, also has an academic position. I have research interests and was an honorary fellow in an academic department. Our Council has representatives from academic departments of general practice there. There is a realisation that expertise exists within academic departments on the research methodology, statistical analysis, publishing of results and most academic departments are extremely encouraging and helpful if full-time service GPs are interested in research ideas and concepts. There is much more collaboration than there was even five or ten years ago. The reasons for this are quite obvious: it is obviously in the academic department's interest to have people coming along with ideas to help write submissions to grant awarding bodies because, as I am sure you are aware, the method by which they are accredited depends very much on published papers

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[Continued]

[Baroness Masham of Ilton *Contd*]

in reputable journals and those only come about whenever research is undertaken.

(*Dr Taylor*) I would just say I think the major contribution that our College makes to research is actually through supporting the publication of the leading journal of academic general practice in the world. It is the most heavily cited journal in the world of general or family practice literature.

Lord Rea

310. Are there any research projects that you can think of at the moment that are particularly concerned with this field of antibiotic prescribing and resistance?

(*Dr Taylor*) We would like to see more research funding. Because, as I understand it, so much research now is directed by the priorities of the research funding bodies, this is not a priority of any of the research councils or of their R&D programmes. I know of people who have had difficulty getting interesting studies funded. For that reason we have actually funded, unusually for us, a study of evaluation of different strategies of antibiotic use which is being done by Dr John Dowell in Dundee. With his permission I could probably give you a copy of that submission.

Chairman

311. That would be very helpful. We have heard before that it is not the easiest thing in the world to get funds for research. Could I just put a final question to you. You have heard that some of us are going to **the USA** in a couple of weeks' time. Is there anything particularly that we should look out for, especially with respect to general practitioner aspects?

(*Dr Taylor*) We did not have a great deal of time to study this particular issue in relation to

antibiotic therapy. I think one of the main points that we want to make is that we are aware that the United States of America in its expenditure on total health care spends a great deal more than this country does. I think our main general point would be that we know also in relation to the proportion of GDP that the United States spends about the same on their limited public health system as we do on the whole of the National Health Service. One of the things we would like to stress is we think that our system is the most efficient and we would not want to see much changed in it. We are aware perhaps that the consumer pressures are greater in America and that gets back to the points we made earlier about the possible effects of that on antibiotic use.

(*Dr Brown*) I think I would really just follow up what the previous witness said and that is the medico-legal implications of withholding certain antibiotics. I would have thought that would be an interesting area to explore with the professionals in the States. The other area that might be worth looking at is to examine the effect that HMOs—health management organisations—have had. There has been an attempt within the States to reduce expenditure on health by bringing practitioners, family physicians, specialists etc into units. One of the main driving forces for that has been a reduction in the cost of the health budget. These are funded usually from some of the health insurance bodies which obviously see a financial benefit in restricting expenditure. As part of that process there is an audit being carried out and quality guidelines, quality markers, are used. I would have thought it interesting to look at the effect of HMOs and whether there is any reduction of the prescription of broad spectrum antibiotics or not.

Chairman] Thank you very much, Dr Taylor and Dr Brown, for coming along.

WEDNESDAY 11 NOVEMBER 1997

Present:

Dixon-Smith, L.	Rea, L.
Jenkin of Roding, L.	Soulsby of Swaffham Prior, L.
Masham of Ilton, B.	(Chairman)
McFarlane, B.	Winston, L.
Perry of Walton, L.	
Platt of Writtle, B.	Phillips of Ellesmere, L.
Porter of Luddenham, L.	

Memorandum by the Association of the British Pharmaceutical Industry

The Association of the British Pharmaceutical Industry (ABPI) is pleased to have been invited to produce written evidence to Sub-Committee 1 of the House of Lords Select Committee on Science and Technology on the topic of "Resistance to Antimicrobial Agents" and later to provide oral evidence to the Committee. The ABPI has approached this request by inviting member companies to answer the nine questions that the Secretariat provided, and what follows are the consolidated replies.

We recognise that the Secretariat has also approached individual companies for their responses and so the replies from the ABPI should be read in conjunction with individual company responses. A list of those companies whose responses have been consolidated in this document are shown in Appendix 1.

Also enclosed are two documents relating to antimicrobials (*not printed*):

An A to Z of British Medicines Research, published by the ABPI.

Hospital Acquired Infection, published by the Office of Health Economics.

1. HOW MUCH EFFORT IS THE INDUSTRY CURRENTLY PUTTING INTO DEVELOPING NEW ANTIBIOTICS?

Does the industry consider that antibiotics have a future, or are the bugs going to win?

The pharmaceutical industry believes very strongly that antibiotics have a future and is currently investing large sums of money in R&D. For example, one company in the field is investing 10-20 per cent of its annual R&D budget on antimicrobials and another company has stated that the research and development of such agents is a strategic priority. Undoubtedly resistance will continue to be a problem and this will necessitate on-going development of newer agents, some of which will be novel.

Unfortunately there are now some pathogenic bacteria for which no adequate therapy is currently available, i.e., some species of *Enterococcus* and the recently reported vancomycin resistant *Staphylococcus aureus*. (ref). The latter of these is particularly of concern as since the 1980s vancomycin has been the only uniformly effective antibiotic available for serious *Staph. aureus* infections. However, the question of whether antibiotics have a future, or are the bugs going to win, is a difficult one to answer in that there will be many battles over a long campaign with winners and losers on both sides. Later in the report we will consider ways in which medicines can be helped to win, but new technologies such as genomics will be crucial.

The British industry is particularly strong in developing new antimicrobials and page 12 of the ABPI A to Z of Medicines lists those companies involved, and the areas in which they are concentrating.

Important factors in the emergence and spread of resistance include: mutation rates in antibiotic target genes in bacteria, the mobility of accessory resistance genes allowing their spread from strain to strain and from commensal to pathogen, the transmission of resistant bacteria from person to person, and the movement of people and food encouraging geographic spread of resistant strains.

2. HOW MUCH EFFORT IS THE INDUSTRY CURRENTLY PUTTING INTO NEW FORMS OF DRUGS TO OVERCOME THE PROBLEM OF RESISTANCE TO ANTIBIOTICS?

What are the lines of attack and what are the prospects of success?

Some of the answers to this question were covered in the answers to Question 1. However, agents currently being developed are in response to the emergence of resistant organisms. These medicines are either new generations of existing classes, completely new classes, or novel medicines with new mechanisms of action. The mainstay of treatment and resistance prevention is efficient antibiotic treatment with eradication of the causative bacteria. Sub-optimal dosage and duration of treatment along with reduced patient compliance can all

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lead to the selection of bacterial populations with reduced susceptibility and thus trigger the development of bacterial resistance. Furthermore, the underlying condition of the patient can be a factor in producing sub-inhibitory drug concentrations, e.g., the presence of pus at the site of infection can reduce penetration.

Improving patient compliance can be brought about by using easy to administer formulations like liquids or slow release tablets necessitating only once or twice daily administration. In the treatment of some fungal infections liposomal formulations have been used. This would theoretically be possible with antibiotics due to the special intrinsic properties of liposomes, particularly in infections caused by intracellular pathogens. These concepts are at present being pursued in early development.

Genomics is being used to pursue this problem by some companies. Targets are being identified which are not shared by microbes and man, and thus ultimately it is hoped that effective therapies can be developed for bacterial or fungal infections which are resistant to many of the current agents. A recent report in the BMJ (ref) indicated a genetic engineering technique which allows resistant bacteria to be rendered drug sensitive. This work developed at Yale University is in the very early phase of development, and if successful it will be several years before a therapeutic tool is developed. Clearly, the industry is hopeful of continuing success in producing efficacious antimicrobials.

3. WHAT SUCCESS IS THE INDUSTRY HAVING IN TACKLING RESISTANCE IN PARASITES (E.G., MALARIA) AND VACCINES?

With the exception of new treatments for HIV, new developments in tackling resistance in parasites and viruses seems to be lagging behind those for anti-microbials. However, in HIV therapy major advances have been made, particularly in the use of triple therapy utilising at least two different classes of medicine simultaneously.

The effect of the new therapies has been to reduce in-patient admissions for AIDS over the last 18 months by 30 per cent in the USA and by up to 50 per cent in the UK.

4. WHAT ARE THE PROSPECTS OF NEW VACCINES?

A vaccine for HIV infection is thought to be only a few years from marketing, assuming that remaining clinical trials are successful.

5. DOES THE INDUSTRY CONSIDER THAT VETERINARY USE OF ANTIBIOTICS CONTRIBUTES TO THE RISE IN RESISTANCE TO ANTIBIOTICS FOR HUMAN USE?

Should veterinary use of antibiotics be further controlled?

Evidence is accumulating suggesting that the use of antibiotics in veterinary practice, particularly for encouraging growth of animals, may contribute to antibiotic resistance in humans. However, clear unequivocal evidence for this correlation does not exist. This therefore needs to be properly investigated and then if necessary Guidelines on the appropriate veterinary use of antibiotics should be considered.

6. DOES THE IRRESPONSIBLE PRESCRIBING OF ANTIBIOTICS FOR HUMAN USE CONTRIBUTE TO THE RISE IN RESISTANCE?

If so, what is the industry doing to encourage responsible prescribing?

Generally, it is accepted that lax prescribing of antibiotics has contributed to the development of antibiotic resistance. Guidelines for the treatment of infections will reduce the incidence of resistant species and the role of industry is to provide adequate information to help in the development of suitable guidelines.

Irresponsible prescribing includes the prescribing of an antibiotic for an infection where an antibiotic is not indicated, e.g., the majority of sore throats; the prescription of an antibiotic for a banal, self-limiting mild condition, e.g., an upper respiratory tract infection; the prescription of an antibiotic at a sub-optimal dose, and the prescription for an antibiotic for too short a treatment duration.

The development of bacterial resistance is usually multifactorial and it is impossible to establish a definite link between antibiotic usage and the emergence of bacterial resistance. However, Spain has the highest consumption of anti-infectives *per capita* in Europe and one of the worst records of antibiotic resistance in Europe.

Antibiotic resistance is a global problem and the key to the problem is better education of health professionals and the public. The industry plays a significant part in this educational process. Improved and harmonised standards of labelling, driven by regulatory requirements are being developed. Some companies sponsor symposia and meetings on rational antibiotic prescribing. The Patient Pack Initiative will ensure that all patients will receive a patient information leaflet with all their medicines. The leaflet for antibiotics will remind patients

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that they should take the medicines as prescribed and must finish the course even though they may well feel better. The reason for this will also be explained.

Another area in which the industry is encouraging responsible prescribing is in conducting surveillance programmes for bacterial sensitivity, ensuring that the right antibiotic is prescribed in certain areas. It has to be remembered that bacterial resistance may vary from geographical area to area. In the developing world, lack of reliable laboratory susceptibility test results, lack of choice of alternative medicines, and uncontrolled usage (particularly South East Asia) means that treatment is frequently sub-optimal.

The messages about not prescribing antibiotics in diseases that are probably viral appears to be getting through to GPs in the UK in that in 1996 antibiotic prescribing dropped by 2.5 million prescriptions. However there were still 51 million prescriptions for antibiotics in the community.

7. WE UNDERSTAND THAT THERE ARE PROPOSALS FOR OVER THE COUNTER ANTIBIOTICS AND WOUND DRESSINGS INCORPORATING ANTIBIOTICS, TO BE SOLD IN THE UK. HOW CAN SUCH PRODUCTS BE MANAGED SO AS NOT TO EXACERBATE THE PROBLEM OF RESISTANCE?

The control of OTC antibiotics will be very difficult due to the requirement to train pharmacists and the public on how to diagnose the relevant condition. This makes a switch questionable. For instance, the majority of sore throats do not require an antibiotic for treatment, but the addition of antibiotics to the pharmacists' armamentarium could increase antibiotic treatment of sore throats, thus leading to the potential for increased antibiotic resistance.

The public already puts considerable pressure on GPs to prescribe antibiotics for self-limiting conditions; this would be applied to pharmacists. However, if this move did occur then very clear guidelines on the sale of antibiotics by pharmacists would have to be introduced and the public would need to be educated to understand that antibiotics were not the panacea for all infections. Furthermore, pharmacists would have to be trained in obtaining microbiological samples in order to maintain epidemiological data about pathogenic bacteria. One area that might be suitable would be in simple cystitis presenting with frequency and dysuria. Failure to respond to treatment or complications like haematuria would require referral to the GP.

8. HOW FAR IS THE INDUSTRY CO-OPERATING WITH THE HEALTH SERVICES, THE PHLS, THE WHO AND OTHER BODIES IN SURVEILLANCE AND INVESTIGATION OF RESISTANCE TO ANTIBIOTICS?

As noted in Question 6, the industry is actively co-operating and indeed promoting surveillance bodies in the monitoring of emerging bacterial resistance. This takes the form of free supplies of sensitivity discs to microbiology laboratories and grants and/or funding of surveillance studies. Some companies are involved in collaborative activities with the WHO in the developing world. Some companies are involved with the WHO net (antibiotic resistance monitoring programmes). One company is acting as co-ordinator of European centres in this project. Another company recently conducted a 56 centre surveillance programme in the UK.

Generally companies believe it is important to interact with established societies and authorities and to that end one of the contributing companies to this document is represented on the PHLS surveillance management team.

The WHO is developing the collection of resistant strains into a strain bank, thus providing a library for further research. This needs active support from Government.

9. WHAT ARE THE INDUSTRY'S RECOMMENDATIONS TO GOVERNMENT AND ITS AGENCIES?

This is a very important issue and Government should actively encourage and support industry and academia to continue researching and developing new agents to address the issue. Government should recognise that this is a global issue and raise the profile of antibiotic resistance as requiring a global strategy. Funding should be provided to the PHLS for national monitoring of resistance patterns long-term as trends can be studied and act as an early warning system.

The Government needs to encourage the responsible and appropriate use of antibiotics and the appropriate use of sensitivity testing. A public education campaign is required to inform the public that self-limiting diseases do not require antibiotic treatment. In considering global strategy, the Government should play a part in applying pressure to those countries where health care is not as advanced as in the western world.

Resistance surveillance is paramount and the Government needs to ensure that this continues in the UK. There is a relatively stable situation in the UK at present with no dramatic trend towards a general increase in resistance rates. This has to be monitored and programmes need to be in place allowing cross-sectional longitudinal analyses in order to recognise changes in the prevalence of bacterial resistance. Furthermore, support for the generation of data highlighting the possible emergence of new resistance mechanisms and linking antibiotic usage figures with resistance development will further enhance our understanding. The Government has an

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opportunity to advance the scientific understanding of the issue by supporting and funding a surveillance study currently being set up by the PHLS and the British Society of Antimicrobial Chemotherapy.

Draft EC proposals to require that surveillance of emergence of resistance to newly registered anti-infectives will be mandatory and will be the responsibility of the relevant pharmaceutical company are misplaced. The Government needs to stress that this is not just the sole responsibility of the pharmaceutical industry, which continues to bring new products to the market in the continuing fight against bacterial resistance.

As antimicrobial resistance is a global problem, overseas aid from the Government needs to concentrate on public health issues, such as clean water, healthy food and sewage disposal. All these factors will reduce the incidence of resistance.

APPENDIX

Companies who provided evidence for this report

Bayer plc
Bristol-Myers Squibb Pharmaceuticals Ltd
Rhone-Poulenc Rorer Ltd
Schering-Plough Ltd
Zeneca Pharmaceuticals

Examination of Witnesses

DR R KUBIN, Clinical Project Leader, Anti-Infectives, Bayer plc, DR M MARRIOTT, International Therapeutics Director, Microbial Disease Research, Glaxo Wellcome, and DR G PATOU, Director and Vice-President, Anti-infective Development, SmithKline Beecham, and DR R TINER, Medical Director, the Association of the British Pharmaceutical Industry, were called in and examined.

Chairman

312. Gentlemen, thank you for coming along to give evidence on this area of resistance to antimicrobial agents. Perhaps you would introduce yourselves.

(Dr Patou) I am Gary Patou. I am responsible for anti-infectives development at SmithKline Beecham Pharmaceuticals.

(Dr Tiner) I am Richard Tiner. I am Medical Director of ABPI.

(Dr Marriott) I am Mike Marriott. I am Antimicrobial Disease Research Director for Glaxo Wellcome, based in Verona, Italy.

(Dr Kubin) My name is Rolf Kubin. I am Senior Clinical Project Leader for Anti-infectives at Bayer plc, pharmaceutical division. As you know, Bayer is an international pharmaceutical chemical company with its base in Germany, but with a broader representation in the United Kingdom too.

313. Do you have an opening statement to make?

(Dr Tiner) No. We have all provided written evidence, my Lord Chairman, and we are happy to answer your questions.

314. Thank you very much for that. We have been told that **developing new antibiotics** has not been your industry's priority for a number of years, yet in your documentation you say that there is currently significant investment in this area. Are the new drugs in prospect likely to be relatively cheap, or more

expensive and how long will they take to come to market?

(Dr Marriott) Perhaps I may respond on behalf of Glaxo Wellcome and the other pharmaceutical companies. If you go back to the early 1980s we were running out of ideas. We had pursued the existing classes of antibiotics about as far as it was possible to take them. However, we were aware, certainly towards the end of the 1980s, of the gradual increase in resistance to antibacterials, and many companies then started to put resource back into antibacterial research. By a happy coincidence this occurred at a time when there was a huge explosion of information, particularly in the field of bacterial genetics. I have lost count of the bacterial genes, genomes that have been entirely sequenced, but it must be at least ten. We know all of the genes present in those pathogenic bacteria. By the end of this century for pretty well every important human bacterial pathogen we will know all the genes which form potential new targets for antibacterials. There have been other developments in technology in terms of the speed and efficiency with which we can test the new antibacterial drugs. That has given us renewed optimism for the future. Richard has some figures to show that the early fruits of that research back in the beginning of the 1990s have already started to bear fruit in terms of the new antibacterial drugs which are currently in development in the United Kingdom.

(Dr Tiner) We have some fairly recent figures which have become available that I put in our

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evidence. I listed the number of companies involved in antimicrobial work. Fifteen per cent of R and D investment in the United States is on anti-infectives and, of course, anything that happens in the United States because of this being a global industry is likely to have a benefit in the United Kingdom as well. Nine per cent of all projects in clinical development are in anti-infectives and over 20 per cent of pre-clinical research in the industry is at present in antimicrobials, so it makes this about the third largest therapeutic class in R and D at the moment. For 1996 these figures have recently become available. There were 312 projects recorded as taking place in antimicrobials, two-thirds of which are in phase one and two of clinical trials, that is the early stages of clinical trials, 68 of those in antibiotics, 19 in antifungals, 43 in non-HIV antivirals, and 82 in vaccines. So you can see the range is fairly wide. With regard to cost, it costs in the region of \$600m to bring a new medicine to market from the time of discovery, and those costs are rapidly increasing. Inevitably, any new medicine that comes on the market is likely to be more expensive than those already there. That would particularly be the case with novel products. The other issue you asked about was the time that these things take to get to the market, in the early 1980s the average time was about 8.3 years for a new medicine to come to market from discovery. At present it is now 10.5, although it is on the way down because the peak was reached in 1989 to 1992 when the average time was 10.9 years. We hope that that timing will get better. With the introduction of the International Conference on Harmonisation we think there is no reason why this cannot improve, particularly as the regulators are part of the ICH process. One of the major problems has been the time taken to get new products through the regulatory process.

315. I am not sure from your reply whether the new drugs will be relatively cheaper or relatively more expensive when they come along?

(Dr Tiner) They are likely to be more expensive than those already on the market, simply because the costs of producing new medicines are going up and some of these are novel products.

Lord Porter of Luddenham

316. I was surprised and pleased about the great effort you referred to that is taking place in research. Is this mainly in a search for new drugs, and if so how novel are they?

(Dr Patou) It is clear that we have not had a major new class of antibiotics for over 20 years and the difficulty that we face is that the existing agents are all permutations on a theme. That means that the bacteria see all these antibiotics in a similar way and are often resistant to many of them. The strategy in industry now is to try to come up with completely new and novel targets. By understanding the genes that are essential to the bacteria's survival we can pull out those genes as targets and use them for a completely new mechanism of action for agents.

317. You see a new phase in development and research?

(Dr Tiner) Yes.

Lord Winston

318. On a point of clarification, you talk about the launch cost of a drug being about \$600m. If regulation were easier and you could shorten that period by a year how much would you save?

(Dr Tiner) There would be some saving. It is difficult to know exactly how much saving there would be. I would be very happy to write to you and send you the answer.

(Dr Kubin) I believe the major saving would not be because of the reduced time needed for development, but in terms of the extended patent time for the company.

Lord Jenkin of Roding

319. Compared with what we have been told in previous evidence, the evidence of the ABPI but more specifically of some of the companies that have given evidence, suggests that for some reason the clinical microbiologists and the people working with them seem to be largely unaware of the huge amount of work going on among the major companies. I have this morning been reading the SmithKline Beecham evidence, which actually spells out, at considerable length, the detailed work with which your company is involved, not only on your own, but in a whole range of other collaborative enterprises. I was particularly struck by what you say about Manhattan Micro. Perhaps you would be able to say a little more about that. Your memorandum goes on to say: "However, the industry's success in realising this potential is dependent, to a large extent, on the commercial and regulatory framework within which the pharmaceutical industry operates." Perhaps you could tell us more about that.

(Dr Patou) Manhattan Micro is an expression that SmithKline Beecham has coined for its major strategic initiative in antibiotic research. The term derives from the term used in the Second World War, the Manhattan Project, which refers to the atomic bomb project which was given the highest priority in the US war effort. Within our company we wanted to give the same urgency to our antibiotic research that has ensued in that spirit. As such, the antibiotic research is structured in a very different way from the rest of the company. We have fully dedicated resources to enable the people working in this research area not to be encumbered with the same administrative issues, for example, that involve other personnel in research. One can just focus on new antibiotic research. The background of getting into this area has been our foray into the whole area of genetics as the basis for the next generations of medicine, and bacterial genomes are particularly amenable to the type of approach that I have described in the document in terms of pulling out the genes that are important to the bugs and then formatting these in a way that allows us to screen hundred of thousands of compounds and chemicals that we have to determine

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which are active against those gene products, and then to bring those forward as drug development candidates. We have given a lot of thought to this because Beecham was a major antibiotic company before the merger, and we are still a major antibiotic company but we have struggled, as you heard earlier, to find scientific leads to enable us to move forward. We have been aware of the growing risk of drug resistance so we have wanted to put the right kind of effort into meeting this growing unmet medical need, which, in a way, is very akin to the industry's response to HIV. It was a tremendous effort to bring forward a whole range of new drugs to meet the community challenge posed by this virus and now we have seen this with resistant bacteria.

(Dr Marriott) It is perfectly true that most of the major pharmaceutical companies have invested heavily in the last five years or so in the antibacterial area. SmithKline Beecham and Glaxo Wellcome have collaborated in sequencing bacterial genetics and sharing that information so that we can speed up and make the process more efficient.

Lord Perry of Walton

320. I am aware of the way you can test many more compounds, but are you able to identify new targets? Is there a limited number of such studies?

(Dr Marriott) We have taken certain bacteria and we have identified all of the essential genes in that bacterium. We know every single gene that the organism needs to survive and grow. Those are the total lists of all the essential targets for antibacterial drugs. We have put those in a book of targets that sits on a PC and you can read the book and select a target and you can screen for inhibitors and potential new drugs. What we have also done, which is something that is completely different and Glaxo Wellcome is not alone in this, is that we have asked the question, is there a completely different approach? Can we look at the genes which are essential for the bacteria that cause disease? If we can inhibit that process we can stop the organisms causing disease and what we will not get is the resistance that occurs to conventional antibiotics in organisms which are incidentally exposed in the mouth, in the gut to antibiotics, because they will be using those genes.

321. When you talk of attacking a gene, what is the relationship between the number of genes and the number of targets? The target has a chemical grouping presumably.

(Dr Marriott) The target is the product of the gene itself. It may be an enzyme or a protein of some sort. There are somewhere between 150 and 200 essential genes in a bacterium such as pneumococcus or E-coli, or whatever. In terms of the genes responsible, for example, for pneumococcus to cause pneumonia we have found somewhere in the region of 100 to 120 genes of which probably a much smaller sub-set of 20 or 25 are absolutely essential.

Baroness Masham of Ilton

322. I would like to ask a question about the **HIV and AIDS** problem world-wide. There are a lot of different antibiotics used. With the triple treatment and

even more drugs, how much evidence is there that resistance to these drugs in the individual will develop; and knowing how the American activists work, has that made drug companies try to get the prices down?

(Dr Marriott) About the triple and quadruple therapies, the evidence at the moment is that it looks very encouraging. I have not seen data in the last couple of months, but at a conference in September the data certainly looked very encouraging indeed. I would hesitate to predict whether resistance will occur to triple and quadruple therapies. We should never under-estimate the ability of a virus to become resistant. In terms of cost every pharmaceutical company wants to make sure that its products are available to those who need them. We do our best to ensure that.

Lord Rea

323. The drugs used for the triple therapy for HIV are very expensive and they are crippling hospital budgets. How much of that cost is reflecting the enormous amount of original research work put in to arrive at the drug, and how much is reflected in the actual costs of production now?

(Dr Marriott) That is not a question that I am able to answer. If your Lordships wish, I can come up with a more considered response to that.

Lord Jenkin of Roding

324. Anybody who has seen, as I have, the literature that has to be produced to the drug regulators before any drug can be licensed would realise there is a huge amount of work and cost that goes into that.

(Dr Marriott) There are huge costs. It is a complicated business discovering and marketing any medicine. As you rightly say, there are costs in discovering the drug, the research that goes into that, the manufacturing and the regulatory aspect, and so on.

Chairman

325. As regards the **licensing arrangements** for new antimicrobials, are they appropriate or should there be a fast track for licensing?

(Dr Patou) The licensing arrangements have served us very well, but they take a considerable period of time and require large numbers of patients for us to assess the safety and the efficacy of the agents we are developing. It might be worth considering the paradigm that we established for HIV which was that if we wanted drugs to reach the market more quickly that we speeded up the regulatory process. I think the level of bacterial resistance that we are now seeing developing in communities and in hospitals certainly merits consideration of whether we want to fast track new antibiotics that are acting by completely novel mechanisms of action and are active against resistant organisms.

326. Do you perceive any potential danger of fast tracking?

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(Dr Patou) Yes, there are potential dangers that one would have to be careful about. Firstly, one would want to ensure it was not a free for all, that one was bringing forward drugs that were of significant medical value. I think that is achievable. Secondly, one would want to be very careful that one was not making a sacrifice in fast tracking in terms of either safety or the full efficacy assessment of the drugs. I think that is manageable.

327. Is there a need for a United Kingdom/European Union orphan drugs programme?

(Dr Tiner) Generally we think it would be useful for such a development. In fact the EC is in the process of developing a document, a directive on orphan drugs. I understand that there is a new draft about to be issued for consultation. The ABPI did have some concerns with the previous draft and we await to see whether those concerns have been addressed. One area was the granting of orphan status within 180 days. We think that that is too long and we think it could be reduced. The fact that the drug should not have received orphan status in the United States or Japan we think is unjustified. We think that if there is to be orphan status available in the European Union then the fact that that particular medicine may already have orphan status in the United States and Japan should not act against it having orphan status in Europe. We believe that simultaneous development in all regions should be encouraged. One problem that the present draft does present to the industry is the issue of commercial sensitivity and we would prefer to see something along the United States lines where application and disclosure are much closer to submission than is proposed in the European draft.

Lord Dixon-Smith

328. How far is relative risk a consideration in the development of drugs, the risk of mortality from the infection against the risk of mortality with the drug?

(Dr Patou) That is a very interesting question. To date we have had the luxury of antibiotics which are essentially a very safe class of drugs, and certainly much safer than many other drugs that we use. There is beginning to be a debate now about whether one should accept a greater side-effect, or safety liability if one is faced with life-threatening diseases and there is simply no other treatment available. It is a path we would not be very keen to go down. It would be much better if we had drugs that were safe.

Lord Perry of Walton

329. Is the industry working on bacteriophage at all?

(Dr Marriott) As far as I am aware no. It is something we have considered certainly but if you consider some of the problems of bacteriophage, which is protein and you take proteins systemically then you develop antibodies to them and you can only use them once to treat a disease and you cannot use them again. They have a number of drawbacks. I think most of us are convinced about using the new genetic information

that will allow us to identify new targets, and perhaps I should have said earlier that, of course, many of these new genes produce proteins which are potential antigens for novel vaccines and prevention is better than cure in many instances. The information that we are generating is such a rich source of information that we should look at that first rather than something like bacteriophage.

330. What about topical use?

(Dr Marriott) Topical use is a possibility but it would require either a large mixture of a number of bacteriophages in order potentially to treat a number of different wound infections or a good diagnosis of what was causing the infection.

Baroness Masham of Ilton

331. The microbiologists have told us that antibiotics can damage the **flora in the gut**. Should there not be more information and other things to go with that to counteract that?

(Dr Marriott) We are requested by regulatory authorities to produce information on the effect of antibiotics on gut flora. Whilst it is true that there is occasionally changes in gut flora which are limited to the duration of treatment, generally speaking you find that the gut flora returns to normal quickly after the antibiotics are stopped.

332. Is it a good thing to take vitamin B with it?

(Dr Marriott) I do not think the effects are great enough to warrant the need for vitamin supplements if the diet is satisfactory.

(Dr Kubin) What we do in the course of developing a new antibacterial is investigate the effect of these antibacterials on the gut flora, not only in the laboratory, but also with human volunteers and we also closely monitor gastro-intestinal side effects in phase two and phase three trials so that we are in a position, by the time of the submission to the regulatory authorities, to say if the activity of the antibacterial against gut bacteria actually translates into clinical effects.

Lord Rea

333. How does the industry defend itself against the charge of **over-enthusiastic salesmanship** without regard to the public health consequences of overuse? Advertising often indicates what an antibiotic *might* be given for, rather than what it should and should not be given for. Does the ABPI have a policy or view on advertising?

(Dr Tiner) The ABPI does have a policy. It has its own code of practice and its own independent body which runs that code of practice. There are relevant parts of the code of practice to advertising and medical representatives, and the most important aspect of that is that any advertisement or anything that is said by medical representatives has to be able to be substantiated by the company and if it is not then that is a breach of the industry code. With regard to the methods of promotion, they must never be such as to bring "discredit upon or reduce confidence in the

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[Lord Rea *Contd*]

pharmaceutical industry". With regard to adverts they must contain at least one indication for use consistent with the summary of product characteristics or the data sheet. Those are approved by the regulators, by either the European regulator or the Medicines Control Agency. With regard to briefing for representatives, the detailed briefings that representatives receive before they go out on the road to meet health professionals have to be available to the Medicine Control Agency and to the industry's code of practice authority for perusal if required. We believe that we provide an independent code of practice for those aspects. The other issue is on the importance of getting information across not just to health professionals but also to the public. A number of companies are now beginning to develop information leaflets for the public, for them to understand that not all illnesses, not all conditions require an antibiotic. We support the rational use of antibiotics, the rational prescribing of antibiotics and we support any attempt to get that message across to the public. We have an example of such a leaflet here, which we would be very happy to leave with you.

(*Dr Patou*) The industry promotes drugs to doctors, and not to the general public, and yet it is the general public that have an expectation often of treatment with an antibiotic when they see their physician. The physician in turn is often under enormous pressure to provide an antibiotic prescription to the patient. With limited time for a consultation and with strong patient expectation, I think we have to look at the responsibility for mis-use, or over-use of antibiotics as a community responsibility involving certainly the industry but also physicians and patients. The leaflet that Dr Tiner was referring to was part of an education campaign that we tried to provide to the general public via their physicians so that the physicians could actually give a leaflet to their patients explaining why they had not received an antibiotic during the consultation. Part of it is community education about the importance of these drugs, for example, when a patient has a viral infection and an antibiotic is not appropriate. In the hospital setting there are different sets of controls and different sets of dynamics and most hospitals now have a committee which is responsible for the selection of all the drugs that are used within the hospital setting, and when they should be used and when they should not be used. Antibiotics would fall within that remit. Very often there will be a clinical microbiologist, a consultant from the hospital with expertise in this area sitting on that hospital committee.

Baroness McFarlane

334. We have been told that often an antibiotic is prescribed before the nature of the bacterium has been identified. We have also been told that a patient may be taken off that particular antibiotic after a very short time and put on another one. How do you regard that practice?

(*Dr Patou*) That is an inevitable consequence of not having sufficiently **rapid and accurate diagnostic tools** to be certain that the patient has a specific

infection and what antibiotics it is likely to be sensitive to at the time of the diagnosis. So both within a hospital and within a community setting an empirical decision is made on the basis, firstly, of whether they have a bacterial infection, whether they have other symptoms and signs, and then secondly based on the understanding of the pattern of resistant bacteria in that hospital or in that community, and if that information is available to help them select the appropriate empirical choice of antibiotic. Subsequently, if the patient fails to respond to treatment or if samples have been taken to enable a definitive bacterial diagnosis to be made, then there is a switch in therapy to a more appropriate therapy. That is how it happens, and I think it is as a consequence of not having the right diagnostic tools at the moment.

Lord Jenkin of Roding

335. Coming back to your evidence, the research in this is not really comparable with other **evidence-based medical research** for a number of reasons that you spell out, particularly that there are no placebos because it is unethical if somebody has an infection to give them a placebo, so you cannot have the trials which would produce evidence-based research. Do you see any way out of that?

(*Dr Patou*) We are beginning to attempt to look at this through the use of computer databases which try to track information, not within a clinical trial setting, but looking at the prescribing patterns of individual patients and the outcomes where it is recorded for the patients, particularly in the United States where there is tremendous centralisation of this information by health care providers (the United States equivalent of the insurance companies, BUPA and so on), where there is information on what prescription a patient received and information as to whether they received another antibiotic for the same episode or indeed whether they were cured. We are trying now to look at these databases to see if we can find real evidence in use rather than in the artificial setting of clinical trials to determine where there are true treatment benefits and where there are not. If there are particular sub-groups of patients whom we should be treating and others that we should not—they may all have a bacterial infection but there may be some who are at risk of complications and others who only have a self-limiting disease—we try to understand this through the use of databases which have hundreds of thousands of patients' data on them.

Lord Rea

336. Where is this population recruited from that forms the denominator?

(*Dr Patou*) In the United States it would be the insurance company records, and something like 50 per cent of the health care would be captured in insurance company databases.

(*Dr Marriott*) From a research perspective, Lord Jenkin is perfectly correct in what he says, that antimicrobial treatment has lagged behind other forms of evidence-based medicine and we do not know the

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bacterium before we start treating. There is information that we are gathering in terms of DNA sequences in bacteria, and we are identifying the specific signals which allow us to pick out different species of bacteria and allow us to say whether or not they carry resistance genes and so on. That information is being used by some very smart diagnostic programmes around the world and that information ultimately ought to be able to translate into a very **rapid diagnosis**, yes, this patient has a bacterium infection, yes, it is resistant to penicillin and then the doctor will have the information needed to treat the patient.

Lord Jenkin of Roding

337. How quickly can that be done?

(*Dr Marriott*) Companies are able to provide that, first of all, with TB, and the first diagnosis of TB is available within four hours of a consultation, and ultimately within 60 minutes.

Baroness Platt of Writtle

338. The ABPI does not favour sale of antibiotics **over the counter (OTC)**. Does the same apply to **prescription by non-doctors**, such as nurses and pharmacists?

(*Dr Tiner*) We are generally opposed to the use of over-the-counter antibiotics. We do accept that a case could be made, for instance, with uncomplicated urinary tract infections. One of the problems about other health professionals being involved in antibiotic prescribing would be that there would need to be specific training set up in order to help those other health professionals make the diagnosis of what the condition was and also there would be a need to look into how the microbiology could be made available to those groups. Obviously, as we have said a few moments ago, the initial treatment would be on an empirical basis, but there would be a need for microbiological testing to be available if required. There are two areas of training specifically that would be needed, that is the use of microbiological techniques and what particular samples would be required and in training of diagnosis. If those could be provided then we could see a case for that.

339. Presumably they would also need training in how to resist pressure when it would be unsuitable?

(*Dr Tiner*) Yes. As an ex-GP myself the pressures of saying, "No, you do not need an antibiotic" in the surgery for certain conditions, for instance sore throats, which is the classic one, mean that it is actually quicker to provide a prescription than to sit down and explain why the patient should not be receiving a prescription. There are pressures and those pressures would automatically be transferred to others in the prescribing situation.

340. More so in a crowded chemist's shop?

(*Dr Tiner*) I think you have hit on a point there. That is important because the other problem that pharmacists would have in this is that of being able to provide an area where the patient in those

circumstances would be able to speak confidentially to the pharmacist, and that is another issue that needs to be addressed in those circumstances.

Baroness Masham of Ilton

341. Surely it goes back to **rapid testing** and whether there was a way of quickly testing for the right antibiotic. We went to King's last week and they said that if only they had a quick test for MRSA—it takes about three days—the pressure on everybody is terrible because of the pressure of getting patients through hospital. You can see how it is easy just to guess the antibiotic, but even more so when there are untrained nurses and pharmacists doing it. It is frightening. Greece has been doing that for years, and they are not really working on it.

(*Dr Marriott*) I think it is perfectly true. We desperately need more evidence-based medicine. I think there are some signs that that will be available. I am told that the TB diagnostic system will be on the market in something like three or four years' time. They are going to take just as long as antimicrobial to design. Beyond that for more routine infections we are probably looking at five to ten years. People are working on it and it will become available in due course.

Chairman

342. Does the industry accept any responsibility for the use in **developing countries** of old, obsolete or inappropriate drugs?

(*Dr Kubin*) As a general remark it can be stated that the member companies of the ABPI do not have different policies for promoting their antibacterials in Europe and North America and in the developing world. We promote antibacterials only in situations where we believe they are indicated and where we have evidence to show that they are appropriate. However, we are aware that there is a lot of misuse of antibacterials, especially in the developing world and one has to say that older and less expensive drugs have been made available to the public there by local generic companies, so it is certainly an area where we cannot exert a lot of influence. We are, however, trying to act against that by, for instance, supporting local bacterial resistance surveillance programmes in the developing world, which most of our member companies involved in this area do. We also try to improve the medical knowledge in these countries by supporting and sponsoring clinical trials, investigating the use of newer and probably more appropriate drugs in the diseases prevalent in these countries, comparing them to older possibly more inappropriate drugs so as to improve our understanding of the best treatment and of the best treatment options in these countries.

Lord Dixon-Smith

343. This is a parallel area because it causes widespread public concern. What steps do your members take when developing **antibiotics for use in**

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[Lord Dixon-Smith *Contd*]

animals to ensure that they will not induce resistance to antibiotics in clinical use?

(*Dr Kubin*) That is a difficult question to answer. There is some evidence that with an increase in the consumption of antibiotics by animals there is also a similar rise of the number of bacterial strains which are resistant to this antibiotic which can be isolated. However, clear evidence that these bacteria cause subsequent infection in humans is lacking, and thus it is difficult for us to give advice that says there is any potential danger for humans of antibiotics which are being produced for animal use. Again it must be stated that most probably resistance surveillance programmes are paramount and these resistance monitoring programmes have to take place in the veterinarian area as well as in the human area.

344. Your opinion at the moment is that the evidence is neither one way nor the other and it simply does not exist?

(*Dr Kubin*) That is right. The problem there is that you will most probably never be in a position to establish the causal relationship between bugs in animals which develop resistance due to antibacterial treatment and infection of humans by these bacteria, although our understanding of this situation may grow by the use of more sophisticated technologies such as DNA and other technologies.

(*Dr Patou*) I think it is something of a smoking gun that one is looking for. One is not clear when the event is occurring of the transfer between animals and humans, and whilst we hunt around for evidence of that after the event has occurred, it is very difficult to establish how that has occurred and when it has occurred. What is clear is that certain patterns of usage of antibiotics in animals do put very high selective pressure on the bacteria to develop resistance, and the long-term use of antibiotics, long-term prophylaxis and the use of very low levels of antibiotics, sub-therapeutic doses which are used, in my company's view, are likely to be important sources of antibiotic resistance in humans.

Lord Jenkin of Roding

345. Would you like to see that being imposed from outside, or do you think that that is a voluntary constraint that the industry ought to adopt?

(*Dr Kubin*) We have considered exactly the issue of using antibiotics for growth promotion within Bayer and clearly we are not promoting any antibiotic use in animals for growth promotion. We have taken a very clear position here. As far as I understand it, this is also the position of the other member companies of the ABPI¹. That is a voluntary decision that we have taken.

Lord Jenkin of Roding] And there are others who do not.

Lord Perry of Walton

346. May I ask about the **surveillance of emergence of resistance** to newly-registered anti-infectives. You say that the whole idea is

misplaced when it is to be the responsibility of the individual companies. Could you explain that?

(*Dr Tiner*) There are two explanations for that really. The first is in the report that I sent in, in our written evidence, I mentioned the draft EC regulation, in fact I should I have written the draft CPMP evidence—Committee for Proprietary Medical Products. The two documents that refer to that have now been finalised and have been issued as complete documents. That section has actually been omitted from the final document. Our point was that we felt it was not just the responsibility of the pharmaceutical industry but actually the responsibility as well of Government to be involved in that process. That was our concern.

Lord Porter of Luddenham

347. On another international matter, we understand that in November 1996, at a meeting in Geneva, the International Federation of Pharmaceutical Manufacturers' Associations and the **World Health Organization** agreed a framework for collaborative efforts in the future to contain the spread of antibiotic-resistant bacteria. Could you tell us something about this and what ABPI has done about it?

(*Dr Tiner*) The first thing to say is that although the meeting took place in November 1996 the final report was not received by the ABPI until 27 August of this year so there was a nine month gap between the meeting taking place and the report being received. Since that time we have had an initial meeting with the Department of Health and we are looking at developing a task group with the Department of Health on antimicrobial resistance. Certainly we plan to meet again when this Committee has made its recommendations. We would wish to be working with the Department on any recommendations that are relevant to the industry in that particular field. What the WHO's paper indicates is that there are a number of things it thinks the industry should be involved in and I am pleased to report the industry is involved in some of those factors. For instance, continuing to develop new drugs, as we have already said, with novel mechanisms. Sponsorship of education for health professionals, the industry is quite heavily involved in that field, particularly in the United Kingdom. The provision of sensitivity tests and financial support and indeed the setting up of some surveillance programmes throughout the world. The encouragement of research into factors which encourage or suppress the emergence of resistance, looking at those areas. Industry improving existing agents by developing new formulations, that was one particular recommendation of that report, not just new medicines but new formulations to improve compliance. That is one area the industry is particularly keen to develop. With all these things we would wish to point out that the document also recognises that with increasing cost containment within health systems throughout the world it becomes increasingly more difficult to bring new and novel medicines to those particular markets. This was an

¹ Note from ABPI: This is not in fact the position of the other member companies of the ABPI.

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DR R KUBIN, DR M MARRIOTT
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[Continued]

[Lord Porter of Luddenham Contd]

issue brought out by that report and it is an issue that is of concern to the industry. My colleagues have other things that they would like to add about the role of the WHO and how we can work with the WHO.

(Dr Marriott) On this question of surveillance, I am a scientist who is charged with trying to discover new antimicrobial drugs. I read a lot in the popular press, the same as I am sure your Lordships do. I would like to know how big a problem this really is. It is very difficult to get hard and fast information that is sufficiently sound to allow us to make strategic judgments in the direction that our research should go. I think there are plenty of opportunities. We all, as companies, fund surveillance programmes to try and provide information to prescribers so they can prescribe more rationally. I would like to see a much more global effort to concentrate this information so that it can be much more useful, much more meaningful. One very trivial thing that needs to be done is to have a standardised susceptibility sensitivity test. Different countries use different methodologies to determine whether a bacteria is sensitive or resistant to an antibiotic. There are differences in the way we do it in the United Kingdom compared to the United States, compared to France, compared to Japan. It makes life very difficult to make comparisons between one country and the next to see just how big a problem this issue really is. I would very much like to see a co-operation between both public and private research to try to get to the root of this problem.

Chairman

348. Is that a job for the World Health Organization?

(Dr Marriott) Notwithstanding the fact that WHO took nine months to get their report out, they are an international body charged with global health issues, it is perfectly reasonable to look to them.

Lord Porter of Luddenham

349. Is the committee you have been talking about that has been set up the body that ought to be looking into this, or is there some other organisation?

(Dr Marriott) The WHO does have WHO NET which is a surveillance programme. I know that our colleagues in Bayer have close collaboration with them, as does SB and so on. By chance they are meeting in Verona next month and they will be guests of Glaxo Wellcome during that visit. We are trying to work closely with them. There is an opportunity for other bodies like the Department of Health, the PHLS and so on, and professional bodies like the BSAC and so on, to co-operate with this venture.

Lord Phillips of Ellesmere

350. It seems like the sort of problem that modern information technology is well designed to help with. What are the inhibitions about using **information technology** in this field?

(Dr Marriott) I can imagine partly the cost because to set up computer networks in order to collect

this information and share it, disseminate it rapidly around the world, is an expensive business.

351. But there are problems of confidentiality and so on that come into it.

(Dr Marriott) I do not think there is any confidential information there at all, no. It is information which everybody needs to know, everybody in the business needs to know.

Baroness Masham of Ilton

352. It must be very difficult getting **information out of the community**. In hospital it is very easy to see that a patient finishes a course. In the community it must be exceedingly difficult. I understand that with tuberculosis they take their course for two or three months and then they feel better so they do not take it any more. Following up in the community is not easy, is it?

(Dr Marriott) It certainly is not easy. One of the programmes that Glaxo Wellcome funds as part of Action TB, which is part of the global programme aimed at TB research, is precisely that, a surveillance programme in South Africa which looks at the epidemiology of resistance to drugs, how do patients take their drugs, how do they react to those drugs, how do you respond to that and so on. It is very important to have that information.

Lord Jenkin of Roding

353. I was slightly surprised by the World Health Organization witnesses who came to give evidence to us when they told us that some people in the industry regard **resistance in moderation as "good for the market"**. Does the ABPI subscribe to that view?

(Dr Patou) The industry tries to develop drugs which meet unmet medical needs and to differentiate their product from a competitor's product. One of the main areas where it is feasible, or has been feasible, to differentiate antibiotics is that they have activity against bugs that another antibiotic does not have activity against. If you have no antibiotic resistance then, other than showing that there are some convenience advantages to your new antibiotic, it is actually very difficult to justify the £375 million of development cost. Clearly there has got to be an unmet need and in the area of microbiology that happens to be drug resistance.

354. That might have been true 20 years ago but manifestly it is not true now because you have got a very real problem to deal with.

(Dr Patou) Absolutely. What we are saying is that we are now very aware of this unmet need and we need to develop new drugs. The way this is worded is perhaps a little pejorative, that it is in the industry's interest to see multi-resistant bugs, but that is not the case. We are there to respond to the medical crisis by trying to develop new drugs that are active against resistant organisms.

*11 November 1997]*DR R KUBIN, DR M MARRIOTT
DR G PATOU and DR R TINER*[Continued]**[Lord Jenkin of Roding Contd]*

355. I was putting it in the form in which it was put to us.

(Dr Patou) I understand that.

Lord Rea

356. It may be pejorative but there may be some validity in that statement.

(Dr Patou) Members of pharmaceutical companies are also susceptible to infection and are members of the community and we on occasion require antibiotics the same as anybody else. It is very difficult to imagine how it would serve our personal interests to see untreatable bacterial infections.

(Dr Kubin) A very final comment. If I could just reword the statement that this may be "good for the market". I think it would be more appropriate to say

that the market desperately requires new antibacterials directed against resistant bacteria.

Chairman

357. Gentlemen, time is up, I am afraid. We have not got round to the fact that some of us are going to **the USA** on Sunday. If there are any points that you feel we should try to take note of, we would very much like to have them.

(Dr Marriott) I would like to leave your Lordships a copy of the report from the New York Health Sciences entitled "Global Public Health Collaboration: Organising for a Time of Renewal". It is a very interesting document. It speaks to setting priorities in health research, it identifies infectious diseases as the number one priority and it talks about collaboration between public and private research.

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Memorandum by Professor R G Finch

PROSPECT OF OVER-THE-COUNTER ANTIBIOTICS

1. INTRODUCTION

1.1 Antibiotic resistance is of national and international concern and is increasing. These concerns extend beyond those professionally involved in the diagnosis and management of infection. There is a large and expanding scientific literature detailing the problem while workshops, task forces and committees of inquiry have been organised by several eminent bodies and governments.

1.2 Antibiotic resistant pathogens have been prevalent in hospitals for several years, particularly within high dependency units such as intensive care, burns, neonatal and transplant units. In the past decade bacterial pathogens responsible for common community acquired infections have also exhibited an increasing frequency of antibiotic resistance, further compromising the activity of many commonly available antibiotics.

1.3 Resistance to antibiotics is detectable among all classes of micro-organisms (viruses, bacteria, fungi, and protozoa). From an international perspective resistance among the agents responsible for malaria and tuberculosis is of particular concern. However, in the United Kingdom the primary concern is the increasing resistance of many common human bacterial pathogens to a variety of antibiotics.

1.4 Resistance to antibiotics among bacteria is a complex problem. In brief, micro-organisms can express a variety of mechanisms whereby they evade antimicrobial inactivation. These include altered penetration (permeability), enzymatic inactivation, altered drug binding or metabolic bypass mechanisms to a particular antibiotic or antibiotics. Antibiotic resistance is also transferable between species and genera. It is important to note that resistance mechanisms not only vary from organism to organism but also geographically.

1.5 It is important to emphasise that the *in-vitro* demonstration of resistance does not necessarily equate with *in-vivo* resistance and therefore failure to respond to treatment. Failure to respond may be due to pharmacokinetic reasons in as far as a drug fails to achieve therapeutic concentrations at the site of a particular infection. For example, many antibiotics are unsuitable to treat bacterial meningitis owing to their inability to penetrate into the cerebrospinal fluid in adequate concentrations. Recent concerns with regard to "penicillin resistant pneumococci" (*Streptococcus pneumoniae*) is a good example in which *in-vitro* resistance does not automatically translate into clinical failure for all pneumococcal infections. High level resistance (MIC > 1mg/l) has clearly been associated with failure of meningitis and otitis media to respond to conventional doses of penicillin. However, pneumococcal pneumonia, caused by similarly "resistant" pneumococcal strains, is still responsive to conventional doses of penicillin.

1.6 The risk to man from the development of antibiotic resistant organisms is also dependent upon their ability to spread, either within the hospital environment or the community at large. Yet organisms differ in their ability to be transmitted from person to person either by direct contact, airborne spread or via inanimate vehicles or food. Once established survival within the normal flora of the skin or gastrointestinal tract is among the more important advantages for transmission of certain pathogens. However, any survival advantage that resistant bacteria possess varies from organism to organism but is often aided by continued or repeated antibiotic exposure.

1.7 Antibiotic resistance and the use of antibacterial agents are closely intertwined. There is evidence from the United Kingdom, Europe and North America linking trends in resistance to antibiotic consumption. Strategies aimed at controlling or reducing antibiotic use vary widely. In medical practice these include policies aimed at selectively reducing the use of certain agents (restricted laboratory reporting of sensitivity data) or prescribing policies whereby certain agents are restricted in their availability or retained for specific serious infections. Education of prescribers figures prominently in undergraduate and postgraduate educational activities. None the less concerns continue to be expressed that antibiotics are over prescribed. When strictly controlled there is evidence to indicate that for certain bacteria and selected antibiotics the trend to increasing antibiotic resistance can be reversed. For example, erythromycin use and *Streptococcus pyogenes*.

1.8 With this background it is therefore appropriate to consider the issues surrounding the potential effects on antibiotic resistance that might arise from any alteration in the licensed arrangements of antibacterial substances whereby they become available to the public without prescription through pharmacy outlets. The arguments and evidence here presented is drawn heavily from a Report of a Working Party of the British Society for Antimicrobial Chemotherapy (BSAC) entitled "Self-medication with antibacterials without prescription" (also called "over the counter (OTC) use"). The expertise of the Working Party includes professionals in microbiology, infectious diseases, general practice, industry, pharmacy and drug regulation. Opinions and comments have also been widely canvassed.

2. CURRENT REGULATORY POSITION OF LICENSED DRUGS

2.1 In the UK medicines are categorised into: POM (prescription only medicine), P (pharmacy) and GSL (general sales list). The definition of these categories is to be found in Table 1 of the Working Party Report. Relatively few countries including those with the European Union possess a P licensing arrangement. A recent

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European Union directive (92/26/EEC) concerning the classification of medicinal products for human use provides two classifications, namely those products subject to medical prescription and medicinal products not subject to medical prescription. Currently efforts are being made to harmonise prescription-only and non-prescription products throughout the EU.

2.2 In the UK an increasing number of drugs have undergone a change in their licensed status from POM to P (five between 1983 and 1990, and 41 since). Drugs with antimicrobial activity currently available for self-medication in the UK are listed in Table 2 of the Working Party Report. The majority of these preparations are for topical application, only fluconazole and the anti-malarial drugs (chloroquine and proguanil) are systemically active. To date, no topical or systemically active antibacterial drug is currently available. However, the more relaxed regulatory climate resulting in changes from POM to P and the growing commercial interest in making available OTC antibiotics lead to the establishment of the Working Party. The report currently remains in draft form. It is anticipated that publication will be in early 1998. Permission to submit this draft document as written evidence has been agreed by the members of the Working Party and approved by the President of the BSAC (Professor R Wise).

3. POTENTIAL BENEFITS OF SELF-MEDICATION THROUGH OTC AVAILABILITY OF ANTIBACTERIAL DRUGS

3.1 A number of practical and theoretical advantages could result from the OTC availability of selected antibacterial agents. Currently the provision of health care is medically led and controlled. Minor infectious illness is often managed by the prescription of an antibiotic. However, such minor illness may arise "out of hours" at weekends or when the patient is away from their normal place of residence. The advantages of making agents available through pharmacies provides greater flexibility and convenience to the public for the management of minor infection. As a consequence, there might be fewer consultations for General Practitioners in relation to minor illness thus allowing more time to deal with more serious health care issues.

3.2 The economic burden from minor illness including infectious illness is substantial. The prompt management of minor illness, apart from its benefits to the individual, may result in the shortening of the period of infectivity as well as speeding return to health and normal daily activities.

3.3 The pharmaceutical industry would be able to exploit a new marketing opportunity, which would have economic benefits beyond the company. It could also result in a transfer of some of the costs of antibacterial drugs away from the hard pressed NHS budget.

4. THE POTENTIAL DISADVANTAGES OF SELF-MEDICATION THROUGH OTC AVAILABILITY OF ANTIBACTERIAL DRUGS

4.1 The potential disadvantages of making antibiotics available for self-medication are several. These include a misdiagnosis or even a missed diagnosis with consequent delays in proper medical management. Furthermore OTC use could increase the risk of adverse drug reactions or interactions and would be of particular concern in the case of children, the elderly, the pregnant and those with pre-existing disease on other medications. Although these agents would only be available through pharmacists as a result of a POM to P change, pharmacists, although highly skilled in medicines, do not function professionally in a manner comparable to a medical practitioner. Their role with regard to OTC medicines is not to make a clinical or more specifically a presumptive microbiological diagnosis but to assist the purchaser in deciding whether the most likely diagnosis is one for which a non-prescription medicine is approved. An additional problem is that few pharmacies currently have facilities which permit sufficient privacy to provide advice in a confidential manner. The pharmacist is also disadvantaged in that while specific contraindications to a drug might be sought from the purchaser, the lack of access to medical records is of concern, especially with regard to the issue of contraindications and the potential for drug interactions. Finally, it will be difficult to guarantee that the purchaser of an OTC medication will be the recipient or that multiple purchases of the same drug will not have been made.

5. CHARACTERISTICS OF AGENTS SUITABLE FOR OTC AVAILABILITY

5.1 Any consideration of a POM to P switch of an antibacterial is the responsibility of the Licensing Authority following a request from the holder of the Marketing Authorisation. Essentially only licensed agents with proven efficacy and safety for a proposed indication at an established dose and frequency would be eligible for consideration. The availability of injectable agents for OTC use is clearly inappropriate and therefore only oral or topical agents are likely to be considered for POM to P. Since drugs would be used empirically, in the absence of any microbiological confirmation of the nature of a particular infection, they should cover the range of likely pathogens responsible for that condition. (Such empirical use reflects the current management of the majority of minor infectious illness requiring antibiotic therapy by general practitioners.) Furthermore there should be sound evidence that the success rate of treatment is high and the potential for adverse reactions including drug interactions is low. In particular the risk of serious toxicity in the young, the elderly and the pregnant requires particular consideration. The patient information leaflet (PIL) supplied with the medication would require careful drafting to aid the patient supplied with the medication would require careful drafting to aid the patient with the diagnosis, identify all contraindications, to use and detail what course of action should be taken in the event of an adverse drug reaction or should symptoms fail to resolve.

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6. POSSIBLE TARGET INFECTIONS

6.1 Among the range of minor infections occurring in the community only a few based on their frequency, predictable microbiological cause and ease of recognition by the public justify consideration for OTC availability. They should not be life-threatening and may well be self-limiting. The diagnosis should be predictably determined on the basis of common symptoms readily identified by the purchaser. For example, these might include: minor skin infections, uncomplicated infections of the lower urinary tract (cystitis) and minor infections of the eye such as conjunctivitis.

6.2 Infections of the respiratory tract present a more difficult problem. Although extremely common many are caused by viruses (sore throat) or predominate in children (middle ear infections) while infections of the lung may occur on a background of pre-existing disease, and be caused by different bacteria that vary according to the exact nature of the infection; it is difficult to predict these variables accurately based on symptoms alone.

7. POTENTIAL IMPACT ON OTC ANTIBIOTIC RESISTANCE

7.1 The potential for increasing antibiotic resistance is clearly a major concern in relation to the possible conversion of POM to P status for of antibacterial agents. Antibiotic use and antibiotic resistance are linked although in an unpredictable manner that differs by drug and organism as well as time and place. However, it is uncommon for resistance to arise in an individual receiving an antibiotic and for this to cause him/her harm. The concern is therefore largely related to the possible ecological effects in which the general pool of antibiotic resistant organisms is increased and the effects this might have on the future management of infections illness in the community.

7.2 While it is unusual for the administration of an antibiotic to give rise to resistance in the target pathogen during therapy, agents can affect the susceptibility of the bacteria which make up the normal flora of the skin and gastrointestinal tract. This in turn could give rise to subsequent infection in an individual or be transmitted to other persons either directly or spread through environmental sources.

7.3 In many developing countries antibiotics are widely available for purchase in an unregulated manner. However, the quality of these products, including the concentration of active drug is poorly controlled. The exact contribution that this state of affairs plays in relation to antibiotic resistance observed in those countries is uncertain although frequently cited as a concern. This contrasts substantially to the potential situation in the UK where only a few agents are likely to be approved for P purchase if at all; the wholesale deregulation of antibiotic is not anticipated.

7.4 Should POM to P be agreed for a specific antibiotic it is likely to result in increased use simply on the basis that it would need to be a commercially viable marketing decision. However, it should be emphasised that the OTC availability of a particular agent is likely to be for specific indications in courses of a single dose to a few days. Long-term use is unlikely to be approved.

7.5 The risk that resistance might arise from OTC use of an antibiotic in an individual is no more likely than if prescribed medically. It could even be theoretically argued that, in the event that only agents with a low potential for inducing antibiotic resistance be granted a P license, the incidence of resistance might decrease. For example, should the aminopenicillin class of drugs be less widely prescribed there might be a reduction in superinfections such as candidosis (thrush) and *Clostridium difficile* associated diarrhoea.

7.6 The question of how could or should antibiotic resistance be monitored in relation to the availability of OTC agents presents considerable difficulties. At present there is no national systematic monitoring arrangement prospectively studying trends in resistance, that might provide robust data on which to make firm judgments. Current data is selective in terms of sampling and is rarely denominator controlled. Furthermore, resistance emerges in different organisms at different rates. To select specific target pathogens and to monitor them longitudinally would present a significant logistical and financial challenge. Furthermore, the interpretation of data so generated would present further difficulties in as far as there are no agreed criteria with regard to what frequency or degree of resistance might result in a recommendation that the availability of a particular drug be restricted because of safety concerns not for the recipient but for the public at large. Here it is interesting to note that agreement has recently been reached and published in the EU guideline (MCA Eurodirect Publication No. EWP/520/96) which recommends that information on susceptibility data of target pathogens be included in the Summary of Product Characteristics for licensed (POM) antibacterial drugs.

8. CONCLUDING REMARKS

8.1 An increasing number of licensed drugs are now available OTC, some of which have antimicrobial activity. There is currently no antibacterial drug licensed for such P use.

8.2 Should pharmaceutical companies request an alteration in the license from POM to P this is likely to affect a relatively small number of agents for specific indications for short-term use. Only indications which can

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be reliably and accurately recognised by the purchaser would deserve consideration. Such infections would be minor and non life-threatening. If approved, drugs would be packaged and marketed as a course containing a patient information leaflet which would detail the indication(s), the symptoms consistent with this self-diagnosis, the list of known side-effects and the contra-indications in terms of age, pre-existing disease or known interactions with other medicines; there would also be advice about what to do should treatment fail or an adverse drug event occur.

8.3 In addition to any directly drug associated safety concerns under a P arrangement, there is the additional concern with regard to the potential impact this might have on antibiotic resistance from increased usage. It has to be accepted that to be commercially viable an OTC agent would be promoted in accordance with the licensed indications.

8.4 With regard to the likelihood of resistance increasing, this is hard to predict with any reliability. It should be carefully considered in relation to individual agents and the indications for which they might be approved. Since an agent would most likely only be approved for short course therapy, the risk of inducing resistance among the recipients is likely to be limited.

8.5 Concerns that increased use in an individual would add to the community pool of antibiotic resistance will remain. Ideally, sensitive monitoring systems to detect antibiotic resistance should be established but would be expensive. There are no established national surveillance systems that would be sufficiently sensitive to identify changes in susceptibility that could be clearly linked to OTC usage. Furthermore, there is no agreed level of *in-vitro* resistance that is accepted by licensing authorities that would automatically result in a recommendation that a license be modified or withdrawn for a particular drug.

8.6 Clearly in the face of such uncertainty and concerns with regard to the safety of OTC availability of antibacterial drugs and antibiotic resistance in particular any major change in the licensed status of such agents presents a dilemma. Any decision for or against such a course of action requires careful judgment of all the issues. It would seem prudent at the present time to address as many of the uncertainties as possible in advance of any move to deregulation in order to improve the knowledge base on which such judgments might be made.

References

1. Acar, J F, and Goldstein, F W Trends in bacterial resistance to flouroquinolones (1997). *Clinical Infectious Diseases* 24 (Suppl. 1): S67-73.
2. Cohen, M L, Epidemiology of drug resistance: implications for a post antimicrobial era (1992). *Science* 257: 1050-1055.
3. Finch, R G, Pneumonia: the impact of antibiotic resistance on its management (1995). *Microbial Drug Resistance* 1(2): 149-158.
4. Pryor, E R and McGowan, J E, Antimicrobial resistance revisited: a public health perspective (1995). *Current Issues in Public Health* 1: 244-250.
5. Seppala, H, Klaukka, T, Vuopio-Varkila, J, Muotiala, A, Helenius, H, Lager, K, Huovinen, P, and the Finnish Study Group for Antimicrobial Resistance. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in Group A Streptococci in Finland (1997). *The New England Journal of Medicine* 337(7): 441-446.

Professor R G Finch

Professor Infectious Diseases, University of Nottingham.

Specialist registration: Internal Medicine/Microbiology/Infectious Diseases

Department of Health Committee on Safety of Medicines (member 1990-92 and 1996-present).

Co-chairmanship of Working Parties.

— Clinical evaluation of antibacterial agents (1989).

— Self-medication with antibacterials without prescription ("over the counter") (1997).

Journal of Antimicrobial Chemotherapy (Editor in Chief 1990-95).

Co-editor "Antibiotic and Chemotherapy" 7th Edition (1997).

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Examination of Witness

PROFESSOR ROGER FINCH, Professor of Infectious Diseases, University of Nottingham, was called in and examined.

Chairman

358. Professor Finch, thank you very much for coming along. Perhaps you would like to introduce yourself and to make any opening comments that you wish to make?

(Professor Finch) I am a Professor of Infectious Diseases at the University of Nottingham. I have a professional background which covers both clinical medicine and microbiology. I have viewed the issue under discussion from both an in-vitro and in-vivo aspect if I might summarise it like that. I have a long professional commitment in the area of antimicrobial chemotherapy. I am sitting on the Committee on Safety of Medicines (Department of Health) at the present moment. I have been editor-in-chief of a major European journal, *The Journal of Antimicrobial Chemotherapy*, until 1995, and I am co-Chairman of the working party looking at the issue of anti-infective drugs and their OTC (over-the-counter) availability.

359. As an opinion leader in anti-infectives, what are your **major clinical concerns** in the short term and in the medium term?

A. In relation to antibiotic resistance I would view this both in terms of community issues and in terms of hospital issues. Within the community there is clearly major concern with regard to the rapid increase of reduced susceptibility of pneumococci to penicillin that is translating into clinical treatment failures when they cause meningitis or middle ear infection. Linked to the issue of meningitis I have early concerns with regard to the other major bacterial cause of meningitis, that is the meningococcus, which is very much in the public mind at the present moment. Although not yet a clinical problem there is evidence to show that some of these organisms are showing reduced susceptibility to penicillin. I think the other area of community concern relates to bacterial enteritis, salmonellosis for example. Quite clearly this is linked to food production and that is a continuing cause of major morbidity, furthermore many patients are admitted to hospital and some die. This is an issue that gives rise to concerns especially now that it is related to antibiotic resistant strains. In the hospital we have a number of problems. MRSA is very familiar to the Committee. Here I would put a rider on this issue in as far as we need better information to indicate which MRSAs are likely to cause clinical disease as opposed to those which simply colonise. In other words, the pedigree to invade is what we need to know about as opposed to simply identifying the biological marker of methicillin resistance. We are also beginning to experience the problem from the United States of VRE, vancomycin-resistant enterococci. However, I would also like to identify the emerging problem of yeast infections such as those caused by candida resistant to azole antibiotics like fluconazole and related drugs; we are seeing this in the HIV population and in those cared for in intensive care units. We will also continue

to experience resistance among intensive care unit organisms such as Gram-negative bacilli.

Baroness Masham of Ilton

360. We went to King's College Hospital last week and there they have pretty good infection control within the hospital. They told us that they have the highest incidence of gonorrhoea in the country in the community around their hospital yet they have not got one **community infection control nurse** so their link with the community was not very good.

A. Traditionally the services for STDs—sexually transmitted diseases—are separate from the main infection control arrangements within a hospital. Clearly the clinics have their own outreach contact tracing arrangements. It is not, I would have thought, a group of professionals that identify conventional infection control practices as being among their major professional activities, they are more involved with contact tracing, providing advice on STDs and their treatment.

Chairman

361. Professor Finch, some of us on this side of the table are having slight difficulty in hearing you.

A. I am sorry. I am suffering from a virus, which is not susceptible to antibiotics!

362. You say: "When strictly controlled, there is evidence to indicate that for certain bacteria and selected antibiotics the trend to increasing **antibiotic resistance can be reversed**." Could you expand on that a little, please?

A. Yes. Most professionals in infection would accept that antibiotic use and resistance are linked, not necessarily always quite transparently. I would like to give you one or two examples. One has been recently published in *The New England Journal of Medicine* which relates to the issue in Finland and an organism called Group A Streptococcus. There was a major problem in 1990 of rapidly increasing resistance to erythromycin. A national campaign was organised to reduce the use of erythromycin to which about 25 per cent of these organisms were resistant. They have shown very clearly that by educating medical staff nationally to observe prescribing guidelines they have actually halved the resistance rates by reducing macrolide use substantially. Another example is from the United States in relation to the issue of multi-drug resistant tuberculosis. This was rising in the early 1990s in centres like New York; again in the early 1990s, and they rediscovered the value of direct observed therapy and, as a consequence, the resistance rates of multi-drug resistant TB have been halved. There are other examples from hospitals where outbreaks of serious Gram-negative infections in intensive care units can be contained by eliminating the antibiotic pressure.

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PROFESSOR ROGER FINCH

[Continued]

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363. Is there a cost-effective strategy to reduce United Kingdom levels of resistance that could be applied?

A. Many people have thought about this for many decades. There is no simple solution. I think it is worth the Committee looking overseas. Here I give one example from Scandinavia. The pattern of use of antibiotics in several of those countries differs from other parts of Europe, particularly as you go from north to south. In Scandinavia they tend to use some of the well-established agents rather than latest agents and they have clear guidelines with regard to what drugs to use for specific indications. Another country that I wish to identify is Holland. Here I would raise the example of the treating of middle ear infection in children. If you look at the United States most children will be treated with an antibiotic for otitis media for ten days, in the United Kingdom similarly but for about five days, in Holland they do not use antibiotics unless there are complications. You have three developed countries viewing the same problem differently and we see lower antibiotic resistance rates in Holland so there must be a message there. Again the Dutch have clear guidelines with regard to the community use of antibiotics which are nationally applied. In the United Kingdom we tend to develop these guidelines at a local level rather than at a national level.

Lord Perry of Walton

364. You say in paragraphs 7.4 and 7.5 that **easier access to antibiotics** is "likely" to increase use; but that this need not aggravate the problems of resistance, and may even reduce them although the effect is "hard to predict". Could you explain why you think that is likely to reduce them?

A. Yes, I agree there appear to be some contradictions between those statements. First of all, I think if we went along the route of OTC antibiotics it is important to say it would not be in the manner that occurs in developing countries whereby somebody can buy a capsule of this or that antibiotic. Antibiotics would only become available in treatment courses for defined indications for a fixed period of time, maybe one tablet for example or a three day or five day course. The issue really is, would resistance be encouraged by this short course therapy?

365. But not all patients buying them would fulfil the requirements.

A. That is one of the concerns, as well as the fact that people could go in and buy multiple packages. On the other hand, we could consider that perhaps drugs could be selected for reluctance for OTC use which would have less impact. In other words, you could choose a drug that came out in the urine but did not impact on the gastro-intestinal tract or skin flora and therefore the pressure to develop resistance could be less. It depends which agents might be licensed for

OTC use. That was one of the concerns of the working party.

Lord Rea

366. Considering the sorts of infections that patients suffer and may go to chemists for, are they not the very ones for which antibiotic use should be discouraged: urinary tract infections, upper respiratory infections? Again in relation to lower respiratory tract infections, I wonder should antibiotics for some of those be allowed over the counter?

A. If we move towards OTC, as is being encouraged by the European Union through various documents concerning the drug regulatory arena, we will need to think very carefully about which target diseases might be considered appropriate. I do not feel that upper respiratory tract infections would be appropriate for the reasons I identify. In the lower respiratory tract, even though a patient may identify symptoms for which an antibiotic might be appropriate, I think there are real medical concerns that the drugs that might become available may not necessarily deal with the variety of infectious problems and their use may mask other disease. Urinary tract infections are identified as a relatively simple area, not without its diagnostic difficulties, but one where the infecting organisms are more predictable, and the drugs that might be used, are prescribed in general practice. The patient would recognise their symptoms and would be able to purchase the same product at their convenience. This seems to be a reasonable condition to consider although there are a number of caveats as I have identified in the document.

367. I am just thinking that the treatment of urinary tract infections is quite a difficult one in general practice because of the rapid rise in resistance to most commonly used antibiotics.

A. Therefore one would have to choose the agent for OTC availability that had a high degree of predictive activity against the target pathogens and had demonstrable efficacy.

368. You would have to change the guidelines quite often because things move so quickly.

A. If this happened at a regulatory level there would have to be a professional response pointing out this issue.

Lord Jenkin of Roding

369. We have had a lot of evidence that has pointed to a clear correlation between the easy availability of antibiotics and the build up of resistance. Spain is a country that has been quoted to us more than once where these drugs are easily available and they have a very much worse resistance problem than we have. It seems to me that you have got an uphill task trying to persuade this Committee, among other bodies, that that is the road we might begin tentatively to walk down.

A. My role here is not to persuade the Committee, my role here is to put the issue into context. There are very real concerns from a medical point of view. The

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[Continued]

[Lord Jenkin of Roding *Contd*]

pressures are coming from the European regulatory arena. Quite clearly industry is perfectly entitled to respond by requesting a change in the licensed status of a agent.

Lord Porter of Luddenham

370. Professor Finch, in your very useful report to us in the last paragraph you are very cautionary really about over-the-counter antibiotics and you say: "as many of the uncertainties as possible" should be addressed "in advance of any move to deregulation in order to improve the knowledge base on which such judgments might be made." This sounds like a very long term process and one wonders whether it will ever come off. What research needs to be done and how long will it take?

A. Essentially a purchaser, not a patient, would be buying a product in response to some symptoms that they recognise and that they think relates to a condition that may respond to an antibiotic. They would be advised by the pharmacist that the drug was appropriate. We have all experienced purchasing items through a pharmacist and, therefore, I think there needs to be a considerable degree of reassurance that the patient's recognition of the symptoms correlates with a medical diagnosis and that this requires an antibiotic. It would be desirable that there be guidelines that allow the pharmacist to advise the purchaser and that these are proven to be highly predictive of the correct diagnosis. I think there are other areas that need to be explored. Drugs would be purchased without access to medical records. Maybe we ought to explore pharmacy linkage with medical records. The purchaser would then be better advised concerning contra-indications or possible inter-reactions that ought arise. It would be desirable to explore issues such as patient education in recognising the relative risks and benefits of purchasing an antibiotic for a particular indication. The other issue is to see if it is possible to evaluate the microbiology of purchasing agents OTC. Could we develop, as we have in general practice, 'spotter' pharmacists that would collect microbiological samples to validate the appropriateness of self-prescribing? I think there are a lot of imponderables about which we have little or no information in relation to OTC availability of antibiotics.

371. Do you see any possibility for deregulation in the foreseeable future in this case, given that there is a very long list of things that have to be done first?

A. There is a discussion document that is currently circulating from the European Union that is a guideline for changing the classification for the supply of medicinal products for human use. This is scheduled to be adopted in February 1998.

Lord Dixon-Smith

372. Is there any country where the prescriber of antibiotics is allowed to provide the antibiotics for profit in a deregulated or an unregulated way and where you would regard the usage of antibiotics as wholly satisfactory?

A. I found that a very challenging question, partly because I am not completely *au fait* with the way medicine is actually delivered throughout the world. I think the implications of the question are that where profit comes into the area of antibiotic prescribing drug usage is likely to increase and, therefore, the potential for drug resistance may be higher. I would have to probably go along with that interpretation. It would be a concern that where drugs are prescribed for profit the tendency would likely be to increase their usage.

373. Can I press this slightly further. Are we heading towards the conclusion that in fact deregulation of supply might actually be too risky?

A. My concern is that if deregulation happens, and this is being encouraged not by the profession but by political sources, it would happen in a manner which is uncontrolled. By that I mean that it would depend on a particular company that owned the licence for a product to apply to the Licensing Authority for a change in the licence status from POM (prescription-only medicine) to P (pharmacy). That would not come about in any structured way and therefore you could actually set a licensing precedent. If one drug is approved, say for urinary tract infections, another company could come along and say "We meet the same criteria" and then you may have drugs which have a greater potential for inducing antibiotic resistance than others. I would be quite concerned about that. There is no arrangement within the regulatory approach to take a global view in terms of what is an appropriate strategy in terms of any structured change in licensing of antibiotic products. It is simply done on the basis of a request by a single company in relation to a specific drug.

Baroness Masham of Ilton

374. The antifungal fluconazole is now available over the counter for use against vaginitis. Is there evidence of the effect on usage? Could you tell us a bit about the history of fluconazole? Why is it available? What is its make-up?

A. Yes. It is an antifungal agent that belongs to the azole class.

375. Is it an antibiotic?

A. It is an antifungal antibiotic. Essentially it deals with a very common problem in the community as you have identified, vaginitis, caused by *Candida*. It is also a drug that we use extensively in hospitals for seriously ill patients who are at risk of fungal disease, for example intensive care unit patients, transplant patients and more particularly HIV patients who are very prone to developing *Candida* particularly of the mouth. It is a drug that has use in treating fairly minor illness through to life-threatening infections. The decision to make this available OTC as a single capsule was based on its safety record and efficacy. Quite clearly the drug has been reasonably successful. You ask about resistance. If we again look overseas: in Spain and Greece, there are concerns with regard to azole resistance among *Candida* but in those countries the drug is available for purchase in an uncontrolled over-the-counter arrangement. It is not sold as a

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[Continued]

[Baroness Masham of Ilton *Contd*]

treatment course. There are early problems of *Candida glabrata* emerging which are resistant to azole. In the United Kingdom there is no evidence to date that the use of a single capsule for *Candida vaginitis* in the community is associated with resistance among *Candida albicans*.

Baroness McFarlane of Llandaff

376. I know that you cannot comment in detail on one particular case but does the current application to provide one UTI treatment over the counter amount to a test case which will set a precedent for other drugs? Or will each such application be treated on its own merits?

A. Essentially every application is dealt with on its own merits but inevitably it would bring about an alteration in the way we view other agents with regard to their OTC availability. Companies can argue on the basis of precedent. Therefore, in some ways I think any deregulation of an antibiotic for a particular indication does in some way set a precedent.

Chairman

377. Could we now turn to other issues. The first is the question of **fast track licensing** for antibiotics. Should the United Kingdom and European Union introduce fast track licensing?

A. In the United Kingdom licensing is now a very rapid process. Most agents, provided there are no complications with the submission, would be assessed and approved or rejected within a period of three to four months. That is remarkably quick recognising the volume of work that is required. With regard to fast tracking, there is the facility to fast track certain agents if they are viewed to be of major public importance. That certainly happens with regard to drugs for HIV for example. So even within a rapid system in the United Kingdom there is still an ability to fast track if it is considered to be appropriate. There are still some delays if the licensing route goes through the European network as opposed to the national network in the United Kingdom. That is something that obviously is being addressed. In some ways I think there is a fast track arrangement already in existence.

378. It is already there?

A. Essentially, yes.

Baroness Masham of Ilton

379. If somebody has a life threatening-condition, can they be offered a drug which is unlicensed?

A. Yes. A drug can be made available on the basis of compassionate use if the physician in his wisdom and in discussion with the producer considers it to be appropriate for the condition.

380. Would that history go back, if it was successful, to the makers?

A. With regard to any drug that is unlicensed, all information on its use would have to be collected and

collected by the company and submitted at the time of licensing.

Chairman

381. Can we turn to **orphan drugs**. Is there a need for a United Kingdom/European Union orphan drug programme?

A. I must confess to not being terribly expert in this area. I know it is under discussion within the European Community. If we are thinking in terms of resistant infections and whether they would be minority infections that would justify orphan drug consideration, I think there would be very few where that would actually need to be considered because the normal licensing process would be adequate to deal with them. There are issues, of course, with regard to patent protection and whether you are patenting the chemical but not necessarily the indication and therefore future new treatments for a particular medication may be developed, so that to give a drug orphan drug status may not always be in the public interest.

382. Finally, what are your views about the use of **antimicrobials in animal husbandry**?

A. I have some views but do not profess to be an expert. Quite clearly antibiotic use in animals is appropriate in terms of reducing suffering with regard to their therapeutic use. That also applies to their prophylactic use although this is contentious. The big concern obviously relates to their use as growth promoters. This accounts for the major use of antibiotics within animal husbandry. Therefore, if we go back to the hypothesis that resistance and volume antibiotic use are clearly associated then there are strong arguments to suggest that growth promotion could be associated with antibiotic resistance. Within the United Kingdom setting I have already stated my concern with regard to the problem of salmonellosis, which is a zoonosis. Clearly salmonella strains are now less susceptible to antibiotics than they were a decade or two ago and these strains can be found in animals. Another zoonosis is campylobacter infection which is the commonest cause of bacterial enteritis in the United Kingdom. Whilst human infection does not require antibiotic treatment in the majority of instances there is evidence for resistance emerging in some European countries to drugs used to treat human disease. With regard to the broad issue of whether one should separate antibiotic classes that are used in man from those which are used in animals, I think prudence would suggest this to be appropriate. We have had the example of the quinolone, enrofloxacin which has been used in animals and has now been withdrawn from use in certain parts of Europe. We also have the glycopeptide, avoparcin, which likewise has given rise to concerns because of its similarity to vancomycin. I think there needs to be greater co-operation between those who are expert in the diagnosis, management and promotion of health in animals and those of us who are concerned with the safety and protection and treatment of human beings. There is the need to be a little bit more transparent in the way such discussions

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are undertaken and what action may be necessary. There is some evidence that improvements in hygiene in animal husbandry as practised in certain parts of Germany can produce as satisfactory results in terms of growth promotion as simply adding antibiotics to the feed.

Lord Rea

383. In your paragraph 7.6 you talk about monitoring and you say: "At present there is no national **systematic monitoring** arrangement prospectively studying trends in resistance," which might be relevant to this particular area, "that might provide robust data on which to make firm judgments. Current data is selective in terms of sampling and is rarely denominator controlled." It seems to me that if we are looking at the whole issue of development of resistance the question of monitoring is of fundamental importance.

A. Absolutely. Essentially information on resistance that is currently available is largely derived from hospitals. There is some information from community practice but in relation to the large number of infections, 90 per cent of all infections are treated in the community, we have very little information on the microbiology in comparison with that from hospitals. In hospital the information that we gather on resistance trends is often derived from a small percentage of the patients, often those in intensive care units, transplant units, burns units, and children's intensive care units. In other words we are getting much information on a population of organisms responsible for infection in patient populations among whom resistance trends can be of concern. I am not sure you can always extrapolate this information to all hospitalised patients and in turn to the community at large. There is a need to be a little bit more robust with regard to the quality of the data that we collect. The other issue is that much of this information simply relates to bacterial isolates. As a clinician I am conscious that the simple isolation of an organism may not necessarily mean it has caused an infection. This difference between a laboratory view and a clinical view of resistance is important. In my clinical practice it is rare for me to be faced, at this present time, with a patient for whom I have no choice in terms of antibiotic therapy. However, viewed from the perspective of the in-vitro trends in resistance there is clearly a concern. Why is there this discrepancy? I think it is in part in terms of the definitions of resistance. Resistance is often defined before a drug is licensed because it needs to be evaluated in relation to some break point; but that break point is rarely revised in the light of overall clinical experience once the drug is licensed.

384. Are there proposals afoot? We have heard from other witnesses that they feel the same way about the need for better monitoring systems to be set up. Do you have any proposals about this?

A. I think surveillance is crucial to developing policies. We need to be clear about what we mean by resistance. There needs to be internationally agreed

definitions. There also needs to be a recognition that an organism can produce infection at many body sites. For example, the pneumococcus causes middle ear infection, pneumonia and meningitis. The dose of penicillin required to cure infection at these sites is quite different, and an argument could be made for different break points for the brain, the lung and the middle ear. Information on the clinical outcome of patients infected with 'resistant' bacteria is also desirable. We also need accurate information on community resistant strains because these infect a larger proportion of the public. There may be an opportunity to develop 'spotter' practices which sample on a more sustained and denominator controlled basis.

Baroness Masham of Ilton

385. Do you think **doctors have enough information** on this? All doctors, GPs and doctors who prescribe in hospital?

A. Most general practitioners lack robust information on antibiotic susceptibility data. Some local laboratories are very good at feeding back information on urinary isolates which can guide treatment choices. On the other hand within the hospital setting we have different populations and ecologies. Patients in the ITU are at risk from different organisms from those, say, on the general medical ward. In other words, making information more unit specific could be helpful. The practice of medicine will largely continue to use antibiotics on an empirical basis, unless microbiological information is more rapidly forthcoming. Even the new diagnostics discussed in the first part of this session, although attractive, are going to be difficult to apply in the community management of infection. The number of infections that are treated in general practice is large and the use of these diagnostic tests in every patient is likely to be prohibitively expensive.

Lord Winston

386. Could we say that, perhaps to follow on what was in the first session, resistance in moderation might be good for academic bacteriologists? **How big a problem** do you think are we facing with resistant strains? This is a question which clearly is a very important one for this Committee. In relative terms medically how important is it?

A. If you look at the last 50 years of antibiotic therapy quite clearly one of the major drivers of change in terms of the pattern of antibiotic choice has been antibiotic resistance. We went from penicillin for staphylococcal infections to flucloxacillin, for example. You can identify other things like safer drugs, greater convenience, etc., but the major driver of change has been changes in susceptibility patterns. There is no reason to believe that we will see a change to this pattern unless perhaps the pattern of antibiotic prescribing changes. We cannot always rely on the pharmaceutical industry to come up with new agents. They have been very creative up to now and maybe the new microbial genomic approach will be successful. I

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[Continued

[Lord Winston Contd]

am sure we will continue to see new problems with regard to drug resistance which will result in further changes in our choice of management. However, each change often brings another problem in its wake. For example, antibiotic use can be complicated by *Clostridium difficile* associated diarrhoea which in turn has been treated with vancomycin. This drug is also widely used to treat hospital staphylococcal infections. Subsequently, we get enterococci resistant to vancomycin. We do need to address the issue of resistance enthusiastically and scientifically and investigate the many issues that we still know very little about. This is where research funding should be more directed at clinical practice. We need new strategies for dealing with infections. We need to understand the best regimen for particular infections, in terms of dose, frequency, duration and endpoints. We should not rely on data produced at the time of the licensing often derived from other countries such as the United States where the practice of medicine differs. For example, drugs are licensed for 14 days whereas in this country we more commonly use them for about seven days or less. Apart from adding to the cost of therapy this will increase the likelihood of antibiotic resistance. We need our own data to support best practice for defining dose, susceptibility definitions and identify the relative risks and benefits of treatment regimens and the impact these might have on antibiotic resistance trends.

Chairman

387. Finally, as you may have heard, a group of us are going to **the USA** on Sunday. Have you any hints for us as to what we should be looking out for and taking particular note of?

A. Yes. I think there are several questions I would go armed with. I would like to hear what action they are taking with regard to antibiotic resistance in hospitals and the community. I would seek out the views of the FDA with regard to the concerns of antibiotic resistance and its current recommendations for testing new agents. I would also be very interested in visiting Atlanta and the Centers for Disease Control (CDC) who, like the PHLS, have a major focus on antibiotic resistance. Linked to the CDC is Emory State University where there is an important research programme called ICARE; this is an in depth survey of the issues surrounding clinical use and antibiotic resistance in hospitals. It is producing very interesting information on drivers of resistance and the ways in which it can be controlled in their health care setting.

388. Do you have a name there for the Emory programme?

A. Professor John McGowan. He is at Emory State University.

389. Thank you.

A. Somewhat tongue in cheek: clearly the United States has one of the most sophisticated health care systems, medically controlled, medically led, pharmacists play a major role in drug usage, all hospitals are accredited for infection control, and there is intensive surveillance. Yet it is one of the countries with a worse record with regard to antibiotic resistance than the United Kingdom. It would be very interesting to seek answers as to why, despite this degree of sophistication, they continue to experience the emergence of new problems: pneumococcal resistant disease, VRE, and multi-drug resistant TB for example.

TUESDAY 25 NOVEMBER 1997

Present:

Dixon-Smith, L.	Rea, L.
Gregson, L.	Soulsby of Swaffham Prior, L.
Jenkin of Roding, L.	(Chairman)
McFarlane of Llandaff, B.	Walton of Detchant, L.
Masham of Ilton, B.	Winston, L.
Perry of Walton, L.	
Platt of Writtle, B.	Phillips of Ellesmere, L.
Porter of Luddenham, L.	

Memorandum by the National Office of Animal Health Limited**1. INTRODUCTION**

NOAH welcomes the opportunity to submit evidence to this Inquiry, and in particular is pleased to be able to address the question of the use of antimicrobials in livestock production.

Animals, like human patients, need and deserve access to a wide range of medicines to prevent and treat disease; for farm animals there is the additional, essential, point that safe, affordable and plentiful food comes from healthy animals. Not only is shortage of food the worst assault on food safety, but the possibility of disease being spread via the produce of diseased animals is, historically, a far greater threat to human health than any of the current concerns.

As with human medicine, in veterinary medicine the availability of antimicrobial products to treat and prevent disease has caused a major revolution in both animal welfare and food production (and the prosperity of farmers). Recollection of post war food shortages, and the frequency of farming business collapse, particularly as a result of poultry flocks being wiped out by epidemics of diseases such as blackhead and coccidiosis, is important if we are to appreciate the widespread benefits of advances in veterinary science.

Today we live in a world with the population exploding at the rate of 100 million new mouths every year. Continuing access by veterinary surgeons and farmers to a full range of essential antibiotics is of vital importance if we are to continue to feed all our people.

Appendix I and II expand on the importance of antibiotics in the continuous fight against animal disease and suffering.

In response to the basic question "can the use of antibiotics in veterinary medicines lead to resistance in bacteria?" the answer must be a scientific "yes". The imposition of chemical pressure on any biological system must inevitably lead to selection of individuals genetically able to survive and multiply. Furthermore, for bacteria, antibiotic resistance is natural. Over aeons bacteria have had to evolve mechanisms to defend themselves against naturally occurring antibiotics. Even today the majority of antibiotics used are of natural origin.

Finally, and returning to NOAH's core subject—animal medicine in the UK, we have to also consider what more should be done to ensure responsible use, but also what would be the *consequences* for veterinary surgeons, farmers and animals if the use of antibiotics for animals was to be severely restricted, as some demand—and whether it would have any practical long-term benefit for human patients and practitioners?

2. USE IN PERSPECTIVE

The market for animal medicines in the UK is small and very diverse—1,900 licensed animal medicines with a total market of less than £360 million, 40 per cent of these sales are for pets and only 60 per cent for all types of food animal treatment. This compares to £6.5 billion spent in the UK on human medicines (i.e., about 30 times the farm animal expenditure). The numbers of animals in Britain is relevant. These are listed as a note to Appendix I.

Although figures on antimicrobial usage on human medicine are difficult to come by, according to the Department of Health, in *England alone*, in 1996, GPs prescribed £174 million worth of antibacterials, via 47 million prescriptions. Even this figure takes no account of the use in hospitals which is the focus of resistance in man. By comparison, in animal medicine for the whole of the UK, all types of antimicrobial, farm *and* pet, totalled less than £80 million and of this, in-feed antibiotic "growth promoters" were only £12 million—hardly evidence of "overuse in animals".

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3. RESPONSIBLE USE

Like human medicines, animal medicines exist to prevent and treat disease and suffering, to influence breeding and growth. The way animal medicine has developed, the way medicines are used, and the future of animal treatment, depends upon a complex interaction of law, economics, social values and veterinary science which must be understood if mistakes, with serious consequences, are to be avoided.

NOAH represents 58 companies to the authorities and to the public. Its members supply 95 per cent of the licensed animal medicines used in the UK, whether for pets or farm animals. NOAH members, in addition to legal requirements, must ensure that their sales staff are trained and registered with the Animal Medicines Training Regulatory Authority (AMTRA) while all their promotional activities (adverts, leaflets, sales staff) are regulated not only by the Medicines Act 1968 but also must comply with the NOAH Code of Practice for the Promotion of Animal Medicines.

The industry is highly regulated. At every stage from initial laboratory work, development trials, marketing authorisation, manufacture, sale, use and post-market residue testing and adverse reacting reporting, the industry and its products are controlled under UK and EU Law and have been for almost 30 years, since the 1968 Medicines Act came in to control human and animal medicines.

Under the Medicines Act, antibiotics for animals are, with a few specialist exceptions (see below), *Prescription Only* medicines which can only be supplied by a veterinary surgeon or by a pharmacist or registered feed compounder responding to a veterinary prescription.

Furthermore all the other controls, familiar to those experienced with human medicine, also apply:

- Licensing of individual products on the basis of Safety, Quality and Efficacy and the independent assessment of data.
- Registration and inspection of manufacturing and wholesalers premises.
- For in-feed medication—registration and inspection of feed compounding premises, including on-farm units, with the RPSGB (Royal Pharmaceutical Society of Great Britain).

In addition to these formal, legal, requirements, the industry has a long history of working both independently and with the authorities to supplement the rule of law with education, publications and codes of practice, as listed in Appendix III.

Although many of the points listed in Appendix III stretch beyond the simple topic of antibiotics, we record them here as evidence of a long history of official action and voluntary industry support for controlled and responsible use of animal medicines in the UK. The success of all these activities can be measured by the extremely low level of animal medicine, including antibiotic, residues in UK meat, eggs and milk and the effective non-existence of any form of black-market or illegal sales system for animal medicines in the UK.

4. CONTROLS OF GROWTH PROMOTERS AND OTHER FEED ADDITIVES

Since 1968 the Medicines Act has regulated all animal medicines, including digestive enhancers, growth promoters and certain other feed additives such as coccidiostats. However under European Law these are regulated as Zootechnical Feed Additives, controlled by Directive 70/524, not as animal medicines controlled by 81/851.

In the UK such "70/524" antibiotics, predominantly used either to improve the efficiency of the animal's digestive system ("growth promoters") or to prevent diseases such as coccidiosis (coccidiostats) while subject to the same regulatory scrutiny as POMs, are classed as "PML" meaning they can be sold without a veterinary prescription but only from premises registered with and inspected by the Royal Pharmaceutical Society of Great Britain (RPSGB). (We note that in human medicine there are moves to allow certain antibiotic preparations to be sold without a medical prescription from pharmacies registered and inspected by the RPSGB.)

This difference is significant—while both the Medicines Act and 81/851 licence the individual branded product 70/524 simply authorises a list of substances—after that there is no specific requirement for feed additives containing a 70/524 substance to be specifically licensed.

Certain MAFF Lawyers have long argued that UK is breaking EU law by requiring products containing 70/524 substances to be licensed under the Medicines Act—although a variety of controls do exist in other member states.

Industry, conversely, has campaigned for 70/524 to be modified so that "Product Specific Approval" (i.e., a form of licence for the *product* not the substance) is introduced. Industry's campaigning has succeeded and under the Fifth Amending Directive to 70/524 a system of product specific approval will be introduced with effect from 1 April 1998. However EU officials confirm that it will be a number of years before all PSA applications can be processed.

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Unfortunately MAFF's Legal Department have chosen this moment to propose that the old Medicines Act licences will be withdrawn for all "70/524" products. Ignoring the Commission's own forecast of several years' delay, *it is proposed that all licensing requirements in the UK will be withdrawn on 1 April 1998!*

Effectively they will be creating a free and uncontrolled market for antibiotic growth promoters in the UK.

NOAH finds this proposal astonishing and irresponsible particularly at a time when the use of antibiotics in this way is under such close scrutiny. We have been arguing, for more than 12 months, that the proposals should be modified so that the UK Medicines Act licence stays in place for each specific product until it has been replaced by a new European "PSA"—this would ensure protection of British consumers and an orderly transition from the old to the new system.

We ask their Lordships to support us in this campaign.

5. PREVENTION BETTER THAN CURE

One frequent criticism of modern farming is the allegation of needless "Mass Medication"; however when there is an outbreak of meningitis in a college, it is accepted medical practice to treat the entire group that has been exposed, even those who are not showing symptoms to avoid spread and to treat those who may be infected before they fall ill.

The treatment of farm animals has many similarities. Livestock, particularly for meat production, are predominantly young, without any lifetime opportunity to acquire natural immunity; sometimes kept in single sex groups and predominantly (unlike school children) generally closely related. Thus if an infectious disease strikes one in a group of pigs (for example) there is a very high probability that the rest of the group, if not already infected, will quickly become so.

For these reasons group treatment of livestock has become accepted practice in veterinary medicines. Not only is this clinically justified, as explained above, but there are other clear benefits:—

- Animal welfare—the remaining animals in the group do not have to fall sick and be manifestly suffering before treatment.
- Disease control—many diseases are spread before gross symptoms appear, so preventative treatment reduces the likelihood of the disease spreading beyond the group.
- Food safety and cost—food is produced from healthy animals in peak condition, and thus operating most efficiently to provide safe food at affordable prices.
- Environment—animal production inevitably impinges on the environment: both in the consumption of resources (land, feed, water, fuel) and the production of pollutants (dung, urine, methane). The greater the efficiency of production from healthy animals, the fewer the environmental demands (see Appendix IV—Feed Additives).
- Responsible medication—in the earliest stages of an infection lower doses of less potent antibiotics can be effective: Once the disease has taken over, higher therapeutic doses may be required—with a much greater risk of resistance transfer to human pathogens (see Appendix V—the Viaene Report).
- In-feed medication—offers the additional benefit of minimising stress (as animals do not have to be handled for dosing or injection), *but* also this demands early treatment as the sickest animals may not be feeding and so will not receive medication.

6. ANTIBIOTICS AND RESISTANCE

As indicated in our introduction, where resistant bacteria exist it is inevitable that they will not be killed by antibiotics and zoonotic infections with antibiotic resistant bacteria will occasionally occur. Nevertheless, we do challenge the assertion that the use of animal medicines has commonly resulted in human pathogens becoming resistant:

Points to consider:—

- (i) The strain of bacterium found in animals is often quite different from those affecting human health. For instance, staphylococci do not cross between man and animals.
- (ii) Although a great deal of attention has been paid in recent years to food poisoning and the allegation that humans have been infected by eating animal produce, it is notable that none of the three major human food poisoning outbreaks of recent years (BSE, salmonella in eggs, and *E. coli* 0157) have been linked in any way to the use of animal medicines, nor have these outbreaks been caused by antibiotic resistant pathogens.

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In spite of many allegations, particularly in Northern Europe, that avoparcin has caused vancomycin resistance (VRE) in human medicine, it is clear that in the country most afflicted with vancomycin resistance in hospitals, the United States of America, avoparcin has never been used in animal production.

Indeed it could be argued that the use of antibiotics in agriculture helps to reduce the transmission of pathogenic bacteria to humans. One wonders how many more salmonella or *E. coli* outbreaks might have occurred if it were not for the beneficial effects of antibiotic treatment of animals.

In one very recent example, it has been recorded that the food poisoning pathogen *clostridium perfringens* is increasing in cases of human infection in Northern Europe. Is it only a coincidence that, following the removal of avoparcin from poultry farming, the level of *C. perfringens* found in chicken faeces has been increasing? This example must, we believe, give rise to the question of whether there is not a greater danger to the human population from food poisoning as a result of the restriction on the use of antibiotic in agriculture than there is from the much more theoretical possibility of resistant bacteria moving from livestock into the human population.

7. THE SPREAD OF DISEASE

As already discussed, all bacteria may develop natural resistance to antibiotics—otherwise they could not survive, and medical science would not require a wide and diverse armoury. If we forget the distinction between “resistant” and “non-resistant” strains then it is easier to consider how disease moves around the world.

Zoonotic disease—affecting man and animals—is complex, the most successful strains have the ability to be carried by both man *and* animals, and for each to infect the other. Food poisoning with strains of salmonella, campylobacter etc., are distressingly common. Food hygiene improvements will remove the organism from the food chain, so any resistance it may carry is then irrelevant. Thus it is equally important to consider the role of food hygiene in the production process, to ensure that bacteria are not spread *with* food, and are killed as food is processed.

8. CONTROL OF RESIDUES

As explained in our summary of industry activities, many initiatives have been designed to educate farmers into better practices which will reduce the level of medicine residues in human food. This is now regulated by EU and international law, which sets Maximum Residue Limits (MRL) for all “pharmacologically active” substances. In the UK the campaign has been successful over many years, with steady reductions in violative samples in the national surveillance programme. UK is unusual in Europe in that we publish our residue test results—the latest VMD report shows a substantial drop in the number of tissues with residues for the first three quarters of 1997 compared to the (already low) equivalent in 1996.

Although the origin of residue control was a desire to prevent direct poisoning of consumers, the benefits are wider and particularly relevant in preventing resistance:

1. Those using medicines, farmers and vets, are forced to think more carefully about medicine use; a complete cultural change has developed so that medicines are used more carefully and responsibly than, say, 25 years ago.
2. Requirements for record keeping, recording of withdrawal periods, quantities used, batch numbers, expiry dates etc. all create a high level awareness of the importance of acting responsibly.
3. Residue control methods based on improved “housekeeping” in the management of animal units further increase awareness while generally improving cleanliness and hence disease spread.
4. The Maximum Residue Limit (MRL) set by the authorities for each active substance is *so low* that there can be no possibility of that concentration inadvertently leading to resistance (see Appendix VI).

(The MRL for chlortetracycline in meat is 1/5000 of the human therapeutic dose—if consuming steak you would have to eat 10,000 kilos to ingest the therapeutic dose! Similarly the MRL for penicillin in milk means that the standard medical dose is equivalent to 500 years adult consumption of milk).

9. CONSEQUENTIAL EFFECTS OF A BAN OF USE OF ANTIBIOTICS IN ANIMALS

While we appreciate that no-one *in the UK* is calling for a total denial of antibiotics for animal treatment, there are those who assert that “Antibiotics are too precious to be given to animals”.

As indicated throughout this paper, access to antibiotics is essential if veterinary surgeons, farmers and other animal owners are to fulfil their moral and legal duty to the animals under their care. One of the “Five Freedoms” defined by the Farm Animal Welfare Council is “Freedom from pain, suffering and disease”.

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Even severely limiting the veterinary armoury, for example by excluding from veterinary therapy of farm animals antibiotics commonly used in human medicine would make veterinary practice and both traditional and modern farming impossible.

Specific causes of concern would be:

- (i) The treatment of mastitis in dairy cattle—some Scandinavian academics have called for this to be banned. Not only is mastitis a painful, debilitating and potentially fatal disease, but it is also contagious within herds. In a new development, milk quality ex-farm is now required to comply with very low “cell counts”. High cell counts occur when the animal is fighting infection in the udder, so severe restriction on the use of antibiotics would make it extremely difficult for farmers to meet these new quality standards. As a recent Swiss paper has shown, antimicrobial resistant bacteria in milk are killed by pasteurisation so there is no risk of transfer to humans via milk.
- (ii) As explained above, in-feed medication with prescription-only antibiotics provides the opportunity for group treatment and prevention. It is physically impossible to treat large numbers of pigs or poultry by other means. (Water medication is used in intensive housing of poultry but is not practical in extensive “free range” systems for pigs or poultry).
- (iii) Use of “Sub-therapeutic” doses of antibiotics as in-feed “growth promoters” and coccidiostats has received much criticism. Use in the UK has been controlled by law for almost 30 years and we have a good record of careful controlled use. Sweden, where growth promoters were banned in 1986, admits to resulting health and welfare problems, which even now require use of unacceptably high doses of zinc oxide in their diet. The productivity and economic costs are, of course, to be added.

In-feed “growth promoters” are more helpfully called “digestive enhancers”—they work not by “stimulating” growth but improving the efficiency with which the animal’s gut digests and absorbs feed. So production is more efficient and less wasteful of resources. The details are contained in Appendix VII.

- (iv) Any ban or restriction based on pressure and sentiment rather than science (the Avoparcin situation) would further undermine respect for and confidence in the EU Licensing process and tend to deter the animal medicine industry from further involvement in the EU.

10. UP TO DATE AND RELEVANT DATA

We are also concerned that judgments are made on the situation as it is today, not on apocryphal report from the past—for example one hears reference to antibiotics being “Sloshed into Lochs” by fish farmers—we are assured by the Scottish Salmon Growers Association that although significant usage of antibiotics was once unavoidable for animal welfare reasons, for the last four years the development of a vaccine for farunculosis has resulted in such a heavy reduction in antibiotic use that some medicine companies are warning that their fish products are no longer commercially viable.

It is equally important that UK should be judged on what happens *here*. The UK has a good record of sensible and effective legislation and industry collaboration, we should not be subjected to further regulations designed to solve problems elsewhere in the world.

When use of antibiotics is implicated in the emergence of a new strain of resistant organism it is essential that scientists put aside prejudices about veterinary versus human medicine and ask *how and where* was the strain first reported and *how and by what* is it being carried around the world? Only if this dispassionate approach is taken can we hope to get to the core of the problem and avoid damaging “innocent bystanders” in the process.

Action by the Industry

The animal health industry is very aware of the need to use antibiotics with due care and prudence. To this end FEDESA (the European Federation of Animal Health Companies) has published a Code of Practice for the use of antibiotics in disease treatment in animals. This has been well received.

The industry is also sponsoring a major surveillance study over two years of the antibacterial sensitivity of *Enterococcus faecium* from animals in six EU countries including the UK. This has been agreed with the EU, is to start at the end of 1997, and will also allow the collection of a range of organisms for future evaluation. This exercise will cost in the region of 1 million dollars, and is seen as an important addition to the available data.

11. CONCLUSION

So, restricting all or part of the range of antibiotics currently available for animals could increase animal suffering and disease, reduce welfare, make greater demands on the environment *and* increase the cost of food—

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and with *absolutely no guarantee* that there would be any improvement in the levels of resistant bacteria in human medicine—particularly in hospitals.

We support the controlled and legal use of antibiotics in animals, and believe that such use should be prudent and informed. To this end we support measures to better educate prescribers and users in avoiding unnecessary use and so maintaining efficacy of these vital medicines.

Appendices:

- I Antibiotics for Animals (*not printed*)
- II “Talking Point” by David Sutton—extract from *Farmers Weekly*—5 September 1997 (*not printed*)
- III 25 years of Voluntary Restraint and Education
- IV Feed Additives (*not printed*)
- V The Swedish Animal Production System. Could it be applied across the European Union? Prof Dr ir Jacques VIAENE, January 1997 (*not printed*)
- VI Maximum Residue Limits (MRLs) and the Safety of food from animals (*not printed*)
- VII Environmental Benefits of Dietary Enhancing Feed Additives (*not printed*)

APPENDIX III

25 Years of Voluntary Restraint and Education

- 1969 The Swann Report which recommended limited antibiotic use as animal growth promoters to those not used in human medicine. When considering reports of antibiotic resistance from other countries, notably the USA, it is important to recognise that although UK and EU adopted “Swann” many other countries did not.
- 1981 Directive EC 81/851—Based on the Medicines Act, the first attempt to harmonise the regulation of animal medicines in Europe by imposing uniform standards of Licensing in every Member state.
- 1986 NOAH published the combined Farmers Code and Medicine Record Booklet, sent free to every UK Livestock Farmer, in collaboration with MAFF.
- 1989 Publication of a joint Pig Industry leaflet on antibiotic feed additives and residues “Feed Additives—Safety First”. (Jointly produced by NOAH/UKASTA/British Pig Association/Federation of Agriculture Co-operatives).
- 1990 NOAH updated its book “The Safe Storage and Handling of Animal Medicines”.
- 1990 Revised EU legislation heralded the creation of the European Medicine Evaluation Agency (EMA) for both human and animal medicines.
- 1992 NOAH produced the “Withdrawal Period” booklet, sent free of charge to all veterinary surgeons. This gathers together withdrawal periods of all livestock medicines on the UK market. Since revised and reissued annually.
VMD, in collaboration with the industry, produced the wallchart “Keep Meat Free of Unacceptable Residues of Veterinary Medicines”.
- 1993 The NOAH Code of Practice for the Promotion of Animal Medicines formed the basis for a European Code introduced by FEDESA, the European Animal Health Federation and now adopted by the National Associations of every member state.
- 1994 NOAH, in conjunction with a number of relevant farming and veterinary organisations, issued Dairy Parlour Chart and “Code of Practice on avoiding antibiotic residues in milk”; sent free of charge to all dairy farmers.
- 1995 NOAH book published “Animal Medicines—A User’s Guide”. The complete review of the law applying to animal medicines after they leave the manufacturers premises. Since adopted has a recommended text for veterinary students.
- 1995 EMA established in London’s Docklands.

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1996 FEDESA introduced its campaign for the responsible use of medicines including "Code of Practice for the Responsible Use of Antibiotics".

VMD produced their leaflet and wallchart "Sulphonamide Medicated Feeds in Pigs".

1997 MAFF to launch a revised version of their 1985 Code "Effective Use of Animal Medicines on Farms" inspired by NOAH following consultation with all the original 15 organisations.

Examination of witnesses

MR PETER WATSON, Chairman, Technical Affairs, NOAH and Registration and Development Manager, Bayer plc, and MR ROGER COOK, Director, National Office of Animal Health Ltd (NOAH); and DR ROBIN BYWATER, Director of Scientific Affairs, Base Business, Pfizer, Chairman of Joint FEFANA/FEDESA Anti-Infective Working Group, were called in and examined; DR JOHAN VANHEMELRIJCK, Secretary-General, FEDESA, was examined.

Chairman

390. May I invite you first to introduce yourselves for the record and, if you would care to, make any opening statement you wish before we proceed to questions?

(Mr Cook) I am Roger Cook, and I am the Director of the National Office of Animal Health which represents the United Kingdom animal medicine industry. My background is in agriculture, but my three colleagues are all veterinary surgeons. Dr Johan Vanhemelrijck is the Secretary-General of our European federation, FEDESA. Dr Robin Bywater is science policy affairs adviser for Pfizer animal health. Mr Peter Watson is registration and development manager for Bayer plc in the United Kingdom. I think that the point that we would like to repeat is the theme of our submission, which is that when looking at this problem of resistance to antimicrobial agents we also need to bear in mind the very good things which antibiotics do in their use in farming and in agriculture, and we believe that it would be a great tragedy if in overreacting to the one problem of resistance we created a whole lot of other problems in relation to animal health and welfare and, indeed, the spread of human disease. In addition to the submission, my Lord Chairman, I have given to the Clerk this morning two further documents. One is a brief statistical summary of the United Kingdom market comparing it to the human and some other industries. You also have something which my European colleagues will refer to later, and that is the European federation's code of practice on the use of animal medicines. Finally, my Lord Chairman, may I just say that we have been trying to get information on the volumes of antibiotic usage in human medicine so that we could present a proper comparative picture to you. Unfortunately it seems that nobody, not even the Department of Health, has those statistics. It may be that your Lordships' influence can bring it to light where we have failed. Thank you, my Lord Chairman.

391. Are there any other opening comments before we go into the questions?

(Dr Vanhemelrijck) My Lord Chairman, thank you for inviting FEDESA to provide oral evidence to the Select Committee on Science and Technology Sub-Committee on resistance to antimicrobial agents.

My intervention will deal with matters of principle concerning the instances that should decide on the criteria and the use of science for the approval of these products. Antimicrobials are individual products which are being divided in classes. The evaluation of the benefits and risks based on the criteria of quality, safety and efficiency in the medicine field, human pharmaceuticals as well as veterinary pharmaceuticals and their nutritional use, has to be done according to established and legal rules and according to procedures defined in the European directives and regulations. Concerning feed additives especially Directive 70/524 has been amended—the fifth amending directive—in order to adapt the legal provisions to the progress of science and technology, preparing for the re-evaluation of the modernised files. In Europe feed additives which are antimicrobials have to be evaluated by the Scientific Committee on Animal Nutrition, SCAN, in order to be accepted or not according to a procedure which is called procedure 3b of the European decision making process. In fact, the same procedure, procedure 3b, is used for the central approval of medicines, human as well as veterinary pharmaceuticals, although the scientific committee is different: one is CPMP, CVMP, and the other one is SCAN. The procedure is intended to allow only those products considered as safe, efficient and of quality. In addition to that, my Lord Chairman, a system of pharmacovigilance is now requested and put in place in order to keep the authorities informed of side effects, non-activity or resistance building. The pharmacovigilance systems is one of the feedback securities that will avoid panic reactions on allegations or suspicions as we are now experiencing. Facts will certainly be more readily available and the relativity of the problem will become more obvious. If new evidence of resistance building or any other side effect is discovered by the very open pharmacovigilance system evaluatory authorities can reassess the file and the data and their advice can be adapted to the new situation. This was done for avoparcin by the Scientific Committee on Animal Nutrition based on the new evidence submitted by the Danish authorities. The SCAN concluded that there was no evidence demanding a ban or a market removal for the products but that, of course, follow up studies had to be performed. Despite that conclusion the

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Member States representatives in the Council chose to ban the product as a precautionary measure. This was Commission Directive 97/6 of 30 June 1997. This is yet another example where the European scientific advice of the appropriate expert committee is not followed. This situation is undermining science and is generating the urge for a multitude of conferences, meetings, congresses and organisations that want to interfere in science. We therefore plead, my Lord Chairman, that the House of Lords try to reinforce the value and the recognition of established scientific risk assessment committees such as the SCAN, CVMP and, indeed, also CPMP. This would allow a proper evaluation of the products by suggesting to the authorities the scientific based risk management procedures and recommending them for the best outcome, taking into account the benefits of the products. The animal health industry, FEDESA, has proposed in 1989 to all partners in the food chain a contract of confidence based on good practices of each partner. We have worked with Lord Plumb and with WHO towards a bureau of food safety and quality. The initiative had the intention better to manage the risk from the farm to the table. We still believe that the answer has to be found in the responsible use of properly licensed products. To stimulate that proper use we have launched at European level codes of good practices and responsible usage codes. This has resulted in a building of consciousness in all partners, and a proper social control on each other's practices. As soon as the tool products disappear for other reasons than quality, safety and efficacy, this social control will disappear.

Lord Jenkin of Roding

392. My Lord Chairman, could we have this in written form?

(*Dr Vanhemelrijck*) It will be delivered, my Lord Chairman.

Chairman

393. Please conclude, Dr Vanhemelrijck?

(*Dr Vanhemelrijck*) My Lord Chairman, FEDESA represents 90 per cent of the veterinary medicines market. The veterinary market is 4 per cent of the human market. The question then is, where is the selective pressure for development of resistance; would risk management and responsible use of hospitals not be the major influence for hospital resistant germs and bacteria and the risk management activities in this field be much more efficacious than jeopardising animal husbandry and animal welfare?

394. Perhaps we could now go into the question, first, of **growth promoters**. You will all be aware of the WHO meeting in Berlin earlier this year, in October. Do you agree with the conclusions that were drawn up at that meeting? The meeting recommended more research and we were wondering what research is now planned or is under way?

(*Mr Cook*) I think that the first thing that it is important to say is that it is essential to study the full

WHO report rather than the press releases which have been rather simplified and even alarmist. We have set out in our submission the situation in the United Kingdom, a long tradition, a long history, of responsible use and detailed controls. We believe that many of those actually preempt the proposals in the WHO report, in other words, we believe that the controls in this country are already very good and perhaps other parts of the world can learn from the British experience. It is also interesting that in the most recent amendments to the feed additive directive, 70/524, the European Union has already preempted quite a number of the WHO proposals and they are already in European law and are in the process of being implemented in the different Member States. We sympathise with a lot of the things that they are saying therefore, but we believe that matters in this country and in Europe are already in hand.

395. The meeting, I seem to recall, proposed a gradual withdrawal of feed additives of an antimicrobial nature which would imply, of course, that in due course research would indicate what could take their place.

(*Dr Bywater*) I was actually present and took part in the WHO meeting in Berlin and it is certainly true that the draft report—the full report, of course, is not yet available but it is expected quite shortly—and conclusions will, I am sure, say exactly that, that they recommended a reduction in the reliance on feed additive antibacterials and as an industry I think that if such products can be replaced by effective alternatives, of course, we are fully supportive of that. My Lord Chairman, you asked about the sort of research that is going on to try to find such alternatives and, indeed, there is quite a lot of work continuing within the industry and elsewhere, particularly looking at alternatives such as the use of probiotics, which is an alternative, and some of these are quite promising. Probiotics have been around for a long time, but they are rather erratic in that finding the right organism for the right species has proved difficult. There is no doubt that if they are properly used and properly chosen and properly researched then they could go some way to replacing feed additive antibacterials. This was one of the subject that the WHO at least addressed indirectly.

(*Mr Cook*) My Lord Chairman, there is one further point on research. We were actually very pleased to see that the WHO clearly accept the concept of growth promotion because they are talking about looking for alternative ways of doing it. In the European Union, of course, we have had a long history of the bans on hormone growth promoters, the ban on BST, the ban on beta agonists and so on, and it is unfortunate perhaps that this political climate in the European Union means that research tends not to be done here but is being done in other parts of the world who are more likely to get the benefit first.

396. Dr Vanhemelrijck mentioned the question of avoparcin and vancomycin. Do you consider that the European Union ban on avoparcin is justified by the evidence of a link with resistance in human enterococci to vancomycin? We understand that the European Union is conducting a monitoring

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programme. I wonder whether you could tell us about that?

(Mr Cook) The simple answer to, "Do we agree", is "no". In our submission we have given quite a number of examples of why we disagree. The classic example is the situation in America where they have vancomycin resistant enterococci without avoparcin ever having been used in animals there, and interestingly you also get the same situation in the horse where VRE is found but avoparcin has never been licensed for horses. We do support, as Dr Vanhemelrijck said, scientific judgments on these things and it was very interesting that the SCAN—the Scientific Committee on Animal Nutrition—rejected calls for a ban on avoparcin, and I quote: "Allegations and suspicions not sufficiently documented to warrant a ban". They tried to look at the science of it and they could not find the science of it. So, we are very disappointed with the ban.

(Dr Vanhemelrijck) My Lord Chairman, if we look at the European Directive 97/6 of 30 June 1997, in fact, the European Union, the Commission, is saying that they do not have enough scientific evidence. They say, "While there are insufficient data to establish conclusively the risk of transfer of resistance invoked by Germany and Denmark, available evidence does not allow the risk to be excluded with certainty." In the absence of further scientific information, which risk can you exclude with certainty, my Lord Chairman? "Various investigations should be undertaken to pinpoint the problem of possible resistance to antibiotics infused by the use of additives in animal feed and transferred to man. A scheme for the surveillance of microbial resistance in animals which receive antibiotics must be swiftly established", etcetera. In fact, therefore, in the absence of the proof of risk the Commission directive is based on the absence of the disproof of the risk, and I think that it is a strange way of making law.

397. I should like to say that some of us have just been to the United States and we have pressed the point on vancomycin resistance occurring there in the absence of avoparcin being used in feed additives. Some of the individuals whom we met maintained that the resistance was in fact coming from Europe via people into the American scene. Would you accept that?

(Mr Cook) My Lord Chairman, I have not heard that allegation before personally.

(Dr Bywater) This has certainly been said, my Lord Chairman, and it is true that any organism can move anywhere on any aeroplane once it is within the intestine, but I think that it is generally accepted that the very considerable problem that they have with VRE in the United States is overwhelmingly the result of excessive use of vancomycin in US hospitals for all kinds of what seem good reasons locally. In Europe, however, where vancomycin has been used to a very much less extent in hospitals and under much more control in hospitals, the problem of VRE is sporadic and by no means large, yet we have had 20 or 30 years of avoparcin being widely used in animals. Therefore, the balance is still quite out of proportion even if,

indeed, an individual may have carried a VRE from Europe in some theoretical sense.

Lord Walton of Detchant

398. My Lord Chairman, after meeting Dr Mudd some months ago I enquired from the Ministry of Agriculture, Fisheries and Food as to whether they believed that an avoparcin ban was justified on scientific evidence, and the conclusion at that time was that it was not, despite which, of course, the European Union went ahead with the ban. Following on with that, how do you rate the evidence that animal use of virginiamycin may have induced resistance in human enterococci to quinupristin or dalfopristin or that the animal use of apramycin may have induced resistance in *Salmonella typhimurium* DT204 to gentamicin? Is there scientific evidence that supports those conclusions, and does it follow that it is likely that a similar ban will be imposed by the European Union on those preparations?

(Dr Bywater) To answer the first question, my Lord Chairman, it is a very similar situation to the one with avoparcin and vancomycin. In fact, what we have is the case of virginiamycin, which is a streptogramin that has been used in animals now for about 30 or so years in much the same way as avoparcin has. Quinupristin/dalfopristin is also a streptogramin combination not yet marketed but shortly to be marketed, but the interesting point is that enterococcus faecium, which is the main target for quinupristin/dalfopristin, in man is almost entirely susceptible because that is why quinupristin/dalfopristin is of interest. Therefore, despite the widespread use in animals the target organism in the human population appears to be susceptible. One therefore has to conclude that whatever virginiamycin has done it has not, as yet anyway, had any influence on the target organism for this new combination.

399. I am sorry, I did not quite follow, did you mean to suggest that that particular enterococcus is non-pathogenic in man?

(Dr Bywater) In general it is a pathogen under some circumstances in immunocompromised and susceptible people.

400. I see, but in general it is non-pathogenic in man?

(Dr Bywater) No, I did not mean that, I meant that it is susceptible to the antibiotic, that is the point, and the resistance has not built up in this particular target organism despite the use of this compound in animals.

Baroness Masham of Ilton

401. My Lord Chairman, if I may just go back to the horse, may I ask what research is being done on why horses harbour strains resistant to vancomycin? Are they resistant to the other antibiotics just mentioned? I actually have a stud and I do observe that vets use an awful lot of antibiotics.

(Mr Cook) My Lord Chairman, I am not sure that any of us here today have the answer to that specific question.

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[Baroness Masham of Ilton Contd]

(Dr Bywater) The particular observation on the horse, if I may answer, my Lord Chairman, was in work carried out in Belgium and it was rather unexpected because no glycopeptide—which is the group from which vancomycin and avoparcin come—as far as anyone knows has ever had any indication in the horse. Therefore, it was quite unexpected and it is not the sort of thing that people would have looked for routinely, but I think, its having been found, other people may well look elsewhere.

402. The Belgians do eat a lot of horsemeat. What are they doing about it?

(Dr Bywater) I do not think they are sitting and worrying too badly about it, but I really could not say more.

Baroness Platt of Writtle

403. Would you like to explain your attitude to the proposed amendment of European Union Directive 70/524 to deregulate growth promoters?

(Mr Cook) My Lord Chairman, I think that there is a slight misunderstanding in the question. We are not concerned that Directive 70/524 is proposing a deregulation; what is being proposed is that in this country the Medicines Act controls on these products are going to be removed in anticipation of new European requirements coming in under the fifth amending directive. Our concern is the question of the management of the transition from one to the other, and what we are saying to the Ministry of Agriculture, Fisheries and Food is that the British licence for the individual product should stay in force until the new European type of licence comes along to replace it.

404. Which will also be product specific, I understand?

(Mr Cook) Exactly. In the meantime a vacuum could be created in which under the present reading of the European legislation materials could enter the British market with much less labelling detail than has been required up until now.

405. So you require a stricter control over a period of years to fit in with the proposed European directive really?

(Dr Bywater) Yes, that is right. We welcome the European directive because it will bring in a level of control across the whole of the European Union, but what we do not want to do is, if you like, to drop the baton while we are moving from British to European legislation.

Lord Dixon-Smith

406. Sweden banned all growth promoters in 1986. Can you identify any consequences? May I ask you whether you would subjectively classify them as gains or losses and would you care to express a view as to whether the balances come out favourably or unfavourably?

(Dr Bywater) My Lord Chairman, I am happy to answer because last week or the week before last the Swedish Minister of Agriculture organised a one day

symposium in Brussels to give an account of what had happened in Sweden and very much to tell everyone the good things that had come from their ban. It was a very interesting day, I think, and there is no doubt that they have to a very large extent managed to exist, if you like, in the absence of these products. However, they were quite clear that it had been a difficult and expensive procedure in the sense that they had had to change their management of animals to quite a large extent—new buildings and so on or new design of buildings—but in particular they accepted that there were disease consequences, animal welfare consequences, particularly in the weaning period in pigs and for poultry, and to overcome these they had had to use alternative feed additives such as adding high concentrations of zinc oxide to pig diets. To this day they have 2,000 parts per million of zinc oxide in pig diets, which would be unacceptable elsewhere in the European Union. Although they are hoping to phase this out, they think that it will perhaps take ten years to do so. Therefore, although they were certainly obviously very supportive of their position, they were equally understanding of the fact that it would be extremely difficult for the rest of the European Union to follow this path and it would take a long time and cost a lot of money.

Chairman

407. Would it be possible to have a copy of those proceedings?

(Dr Bywater) My Lord Chairman, there is a report produced by the Swedish Government and I can certainly arrange to have a copy sent to you. It is quite a thick document. What it is in fact, my Lord Chairman, is the submission from the Swedish Government to the European Union justifying their derogation from the directive which would otherwise have them use feed additives like everyone else.

408. We would need only one copy.

(Dr Bywater) I am sure that that can be arranged, my Lord Chairman

409. Yes, Dr Vanhemelrijck?

(Dr Vanhemelrijck) My Lord Chairman, perhaps I could just add that the question can also be turned around and it can be asked, can the Swedish model be applied in Europe in the actual circumstances? Sweden at the time in 1986 when they decided this—and they said at the conference that they decided it not on scientific evidence but because there had been a public debate on animal production—had not signed the GATT. They were also not a member of the European Union, so you could talk about “the island, Sweden”, on animal husbandry: they were protected. Now coming into the European Union gives them a problem because they now have to compete with the other farmers of the European Union. The farmers of the European Union themselves have to compete with the world because each of the countries of the European Union has signed the GATT agreement. Giving a competitive disadvantage to the farmers and not being able to compensate for it, because that is also forbidden by the GATT, more subsidies, is a difficulty

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and a burden that you put on animal husbandry, so the adverse economic effects are something that is of importance and of more importance today here than they were in 1986 in Sweden because they could compensate with subsidies. If also you look at their antibiotics usage and you calculate zinc oxide as being an antibiotic, which it is, in fact—an antimicrobial certainly—then their usage has not been reduced. In fact, by using the therapeutic product you could say that they use the more modern product which is giving better effect on a fewer milligrams per kilogram basis. The zinc oxide gives them a lot of environmental problems and despite those environmental problems farmers are asking for ten years' transition to get rid of the last one, and then they have the trading disadvantages.

410. I think that I have got a picture now of some of the possible disadvantages. May I just ask what the gains have been, if any?

(*Dr Vanhemelrijck*) My Lord Chairman, according to the Swedish conference and the ministry, the gain has been certainly that there is no possibility any more officially to hide bad management by the use of antibiotics, and I think that is a major gain of consumer confidence.

Lord Rea

411. You mentioned the economic disadvantages. Are you talking about slower growth of animals, or increased mortality of young animals? It cannot surely be the cost of the zinc oxide, which I should have thought would be quite cheap?

(*Dr Bywater*) My Lord Chairman, I think there is no doubt that there is an economic loss because animals will grow more slowly in the absence of these compounds, but the main reason for using them is the better productivity. However, that better productivity is also partly for health and welfare which makes them more liable to survive.

Lord Phillips of Ellesmere

412. Could you tell us something about the fundamental understanding of the processes by which these growth promoters work?

(*Dr Bywater*) There is no fundamental and absolutely clearly defined method by which they work, but there are quite a number of very clear observations which shed light on it. There is no doubt that the bacterial population within the small intestine of a monogastric animal will itself have a nutritional requirement which will take in part of the dietary intake and use it for itself rather than for the animal, and that we believe is a part of what is happening. However one of the interesting observations that you see in an animal that is fed an antibacterial growth promoter is that the intestinal structure is different. The intestine, as your Lords are aware, has a layer of villi which increase the surface area: they are finger-like projections with enzymes, and they are where the absorption and the digestion occurs. If you look at an animal with a growth promoter in its diet, these are

much longer and thinner and obviously more efficient. Interestingly, if you look at a germ free animal you see exactly the same only even more so, a very thin intestine with these long, slender villi. My own particular preference about this is that within the intestinal flora there are organisms which release toxins which, if you like, irritate the lining of the intestine and damage it in a subtle way so that instead of being long and thin the villi are short and stumpy and thick and, frankly, less efficient. That I think is the way in which these compounds work. Particularly which organism is involved frankly is not known because the anaerobic microflora within the intestine—and even in the human intestine, as you are well aware—is extremely complex and, frankly, it is not well understood. That I think is the most likely explanation.

Lord Winston

413. What research is being done to evaluate this?

(*Dr Bywater*) There is research going on, my Lord Chairman. It is a sort of physiological approach to the intestine. There is work that has been going on for some years now.

414. Where?

(*Dr Bywater*) Newcastle University, and certainly elsewhere, but Newcastle has been a centre of excellence for this sort of work to try to understand what these compounds are doing.

Lord Phillips of Ellesmere]My Lord Chairman, in the light of the precautionary principle I wonder whether the witnesses would say that given the lack of fundamental understanding there was some risk in proceeding in using these growth promoters since we simply do not know what is happening.

Lord Porter of Luddenham

415. Or, to put it another way, would you agree that there is no need whatever for growth promoters and it is purely an economic advantage?

(*Dr Bywater*) No doubt there is an economic advantage, and that is the prime reason why they are being used, and let us be quite honest about that. There is also an animal welfare advantage, which I think was illustrated by what has happened in Sweden. If you take them away you have disease and animal welfare problems. So the two are there together, but it is no secret that the reason for using them is economic.

416. My Lord Chairman, why did the Swedes decide that they would rather give up using these growth promoters?

(*Dr Bywater*) It was a matter of principle for them. They decided that they had, and have, a rather small industry and it was for them practicable to take the action that they did on a matter of principle.

417. But was the principle concerned with unforeseeable risks?

(*Dr Bywater*) My Lord Chairman, I do not think that that came out in the way that they described it. It

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was a matter of principle that they would like to move away from these compounds, and so they did.

Lord Perry of Walton

418. My Lord Chairman, I thought I read in the submission that the doses of antibiotic were sub-therapeutic. How could their use be said to be for animal welfare?

(*Dr Bywater*) My Lord Chairman, they are sub-therapeutic in the sense that they are not present in concentrations that would normally be expected to treat disease. However, the reality appears to be that if you take them away there is an increase in disease which occurs. That is not the reason primarily why they are being used. As I said, that is economic. The Swedish experience and certainly the experience that people have had elsewhere is that there are disease consequences, particularly in the post-weaning period in the pig and particularly to do with necrotic enteritis infection in broilers where there appears to be at least some link which may be indirect in disease control.

Baroness Masham of Ilton

419. By how much has the disease gone up since Sweden stopped using antibiotics?

(*Dr Bywater*) Some calculations show that they had quite considerable losses. One of the consequences of the removal of these, of course, is that the use of therapeutic antibiotics increases to treat the disease which occurs in the absence of the feed additive compounds.

Lord Dixon-Smith

420. Just to go back, my Lord Chairman, it has to be the fact that for a very long time animal husbandry and agriculture in general managed, I will not say happily, but they managed, without these substances. Can you speculate as to what the consequences would have been if they had never been used? Presumably animal numbers would have to be that much greater at least at birth in order to supply markets?

(*Dr Bywater*) My Lord Chairman, I think undoubtedly that if they had never been used, in order to have the animal production that we have at the moment—and, dare I say, need at the moment—then the costs would be greater and the number of animals would be greater at least, as you say, at birth, but nothing is essential, nothing is irreplaceable; it is simply that it would be difficult.

Lord Walton of Detchant

421. My Lord Chairman, we have had a paper based upon a study that was carried out by the Department of Agricultural Economics at the University of Ghent which indicates that the Swedish decision has resulted in lower production efficiency and increased costs, as well as the increased use of therapeutic levels of antibiotics, and it has imposed a heavy economic burden on consumers and farmers alike. I think that it is important perhaps just to make

those points, my Lord Chairman, that have been clearly brought to our attention.

(*Mr Cook*) Thank you, yes, it is the overall benefit, and two things need to be considered as well. First of all, as is indicated in our submission in one of the appendices, there is an important environmental benefit that comes out of the more efficient use of animal feed. We are using less feed, producing less dung and so on, for the same amount of production. The other thing, my Lord Chairman, is that it has to be said—and I believe that it is there in Professor Viaene's report—that Sweden does not feed all its people. It has to import from other European countries that use more conventional methods to maintain the food supply for its own citizens.

Baroness McFarlane of Llandaff

422. In your evidence you defend **prophylaxis**—that prevention is better than cure. Would you accept that some farmers overdo it? What does the industry do to encourage best practice?

(*Mr Watson*) My Lord Chairman, before we can really answer that I think that we need to define prophylaxis as we see it very clearly because there has been a lot of confusion about this particular area. Some people would include in prophylaxis the practice in veterinary medicine of treating animals in close contact with a disease. Animals are not kept as individuals, not as humans would be, but they are often in pens of five or ten animals. If two or three of those animals are infected, the likelihood is that many, if not all, of the others will be in a subclinical phase of that disease progress and the whole pen is treated, if you like, like one individual animal unit. That in our opinion is not a prophylactic use of a drug; it is a therapeutic use of a drug. Prophylaxis comes down to using a medicine in a way to protect against a problem which you perceive will happen in the future. A typical example would be diarrhoea in piglets after weaning, which can be a big problem on some farms. There are some management factors clearly involved in this, but you know that two days after you wean the pigs they will develop diarrhoea, and some will become very ill. You include a therapeutic drug over that period to prevent that happening, and that is what we understand as prophylaxis. It also in my opinion includes things like vaccination to prevent disease in the first place, the clear use of a drug in this area. I think therefore that we need to be very clear on that. In the case of vaccination I think that we would all agree that prevention is better than cure in these circumstances. I think that prophylaxis in the true sense as I have just defined it, my Lord Chairman, is not maybe the most desirable practice but the veterinarian on the ground has a problem when he is dealing with it and has to make up his mind on a case by case basis whether it may be appropriate. I do not think that any of us sitting here would agree that using it on a long term basis to overcome poor management techniques is an appropriate or proper use of such drugs, but on an individual case by case basis it may be necessary. I think that is all on that. Then on the question, would I accept that some farmers overdo it, I think that that is

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possibly the case, and we do not defend that. As far as what we do to encourage best practice is concerned, perhaps I may hand back to my colleague, Roger Cook.

(*Mr Cook*) My Lord Chairman, I think that it is important on this question of the subject of whether farmers overdo it to recognise that we are talking about prescription-only medicines only used on the farm with the involvement and approval of veterinary surgeons. Yes, my Lord Chairman, some farmers do overdo it, some doctors overdo it, some boxing promoters overdo it: people in all walks of life overdo things. As to what we do to encourage best practice, we have indicated in our appendix III a long list of the things that industry has done, often in co-operation with other bodies, organisations and the authorities, and that will continue. In addition may I draw your Lordships' attention to the FEDESA document (on responsible use of animal medicines) that I passed round, and maybe Dr Bywater or Dr Vanhemelrijck would like to comment on that.

(*Dr Bywater*) My Lord Chairman, this is an initiative that we took within FEDESA in a committee which I chair on anti-infective agents. We absolutely agree with the point that overuse does occur and we want to discourage that by correct and appropriate use. The code of practice, the guideline, is really a way of trying to get people to use the things a little more thoughtfully with more precise diagnosis. This does not exclude the judicious use of prophylaxis or what we sometimes term metaphylaxis, for animals in contact with disease. I think that if they are properly used and if they are appropriately used that would result in a reduction in the amount that was actually given to animals and, if that is the reason for doing it, then we support it.

Chairman

423. May I just ask where this document is going to?

(*Dr Bywater*) My Lord Chairman, it has been circulated certainly within the animal health industry, but we hope to get it more widely circulated through the British Veterinary Association and actual practitioner organisations and, if necessary—we have had some input from the practitioner groups, but we would like to have more—redraft it with their influence and therefore make it, we hope, even more acceptable to the practitioner because that is the person who we are trying primarily to influence.

(*Dr Vanhemelrijck*) My Lord Chairman, this has been publicly made available and we are negotiating with the practitioners at European level and with the European Union veterinary practitioners and they are now studying the dossier on responsible use in order to make sure that all their members do agree and, once they agree, then it will be put into operation at the local level.

Lord Jenkin of Roding

424. My Lord Chairman, may we turn now to what is really at the centre of this argument, that is, the question of **whether the use of antibiotics in animal**

husbandry is actually contributing to resistance in humans. You come, if I may say so, at the end of a long string of witnesses that we have been seeing since the summer and it was very helpful right at the beginning that the PR firm acting for the National Office of Animal Health, John Kendall Associates, sent us a document which we have been able to take account of in the course of our examining other witnesses; in particular, we noted the conclusion that you had at the end of one of your leaflets that there is "no proven link between antibiotic usage in farm animal livestock and the incidence of resistance in man". We have tried out that proposition on virtually every expert witness that we have seen, mainly clinical microbiologists and microbiologists who work in laboratories and universities and so on, and with one exception they have said that proven is the key word. They have all regarded that statement as one to be greeted with amazement and incredulity—"How can anybody say that in the light of what appears to be the overwhelming link?" Now that is the case which you have to meet, and I am going to put to you. One particular case has been drawn to our attention, and that is that the veterinary use of enrofloxacin may have induced resistance in *Salmonella*, *E.coli* and *campylobacter* to ciprofloxacin. Now we have had the evidence that that appears to be established. What is your reaction to that?

(*Mr Watson*) My Lord Chairman, this may take a little bit of time to go into. It is obviously a very wide question. The first point that I think I would like to make is that due to other legislation in the European Union a very widely used antimicrobial for the control of some of these diseases, particularly *Salmonella*, that is, Funazolidone, was withdrawn from the market fairly recently. That is because of its lack of ability to obtain the maximum residue limits (MRLs) for use in animals intended for human consumption. That inevitably has thrown more pressure and more exposure if you like onto those other antimicrobials which remain on the market. That is the first point, my Lord Chairman. The second point, and I think that I would like to broaden your question—you mentioned specifically two active ingredients—is that I think it is fair to point out that currently in the United Kingdom there are four fluoroquinolones licensed for use in veterinary medicine and in the European Union there are five MRLs set for the use of fluoroquinolones in animals and, of course, there is more than one fluoroquinolone used in human medicine. On the three species to which you have drawn attention, may I start with *Salmonella*. It is true, as I think we said in our submission, that if you apply a selection pressure to any natural organism it will adapt to meet that selection pressure. The argument that we are talking about here is, how quickly does that happen, how serious are the other consequences and how can we manage that situation. With *Salmonella typhimurium*, which is one of the organisms most exposed to this discussion, we know with quinolones that approximately 10 per cent of strains exposed in test tubes to quinolones will have a small shift in their sensitivity, but what does not happen very commonly, if at all, is that that shift becomes clinically resistant.

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The point that I would like to make here very clearly, my Lord Chairman, is again confusion about the term resistance. You can certainly demonstrate with some of these organisms, *Salmonella*, for example, a change in the sensitivity patterns, in other words, they are somewhat less sensitive than they were prior to being selected. However, the sensitivity pattern is still well within the accepted range of normal therapeutically achievable concentrations of these drugs, both in animals and in humans, that is to say, they are clinically sensitive even though microbiologically there has been a small change. In addition we have other evidence that we have looked at. A recent survey of over 1,000 strains of bovine origin from Northern Ireland were examined for resistance to fluoroquinolones. None were discovered despite the fact that in the south of Ireland—I know that it is a different country, but there is a lot of movement across the border—fluoroquinolones have been licensed for use in cattle since 1986, and they have been used quite widely, so that is another piece of evidence there. Again looking at pharmacovigilance, which has also been mentioned, in the United Kingdom we have had a fairly good pharmacovigilance system in place for many years. We are not aware of a clinical resistance to fluoroquinolone therapy in some animals in the United Kingdom. Clearly on-going monitoring of that situation is required, and that is being undertaken. I think with *Salmonella* a joint development is already set between industry, the veterinarian in practice and also the farmers to try to minimise any impact that it may have. In the long term, my Lord Chairman, I think that the development of biological vaccines against some of these diseases may also dramatically reduce our need, and there is a veterinary need, to treat *Salmonellosis* in animals. It is a severe, debilitating, life threatening condition, particularly in calves, and therapy is indicated on welfare grounds.

425. We would all hope that you are right on that last point, but could you offer an explanation as to why all the senior microbiologists, (the clinicians, one after another, simply do not appear to accept the argument that you have been putting to us. Why do you find yourselves, as it were, a voice crying in the wilderness with so much medical evidence against you?

(*Mr Cook*) My Lord Chairman, I think, with respect, medical evidence is not necessarily the same as conjecture.

426. All right, prejudice then?

(*Mr Cook*) One is reminded of Luke, chapter 4, "Physician, heal thyself". I mentioned in my introduction that it is very difficult to get statistics on human usage of antibiotics in this country, but we have found with quinolones, the subject of this question, that the human GP in England—so that is not hospitals, that is not Scotland or Wales or Northern Ireland—in 1996 used five times as much quinolone as did the entire veterinary profession in the entire United Kingdom. This is why I think that it is so very important that these statistics are revealed so that we can have a proper examination of what is really happening.

427. So you are accusing doctors of wanting to continue their treatments, recognising that they build up resistance and blaming you for the result?

(*Mr Cook*) My Lord Chairman, I think that it would be better to say that we would like to put our house in order.

Lord Porter of Luddenham

428. If I may just come in here on a point of statistics, and this comes out of your very useful figures and some figures that you gave us earlier, the figures that you have just given us of comparisons between human and animal are comparisons of cost, are they not?

(*Mr Cook*) No, my Lord Chairman, those last figures were tonnages. Human doctors in England use nine tonnes of active ingredient of quinolone compared to 1.7 tonnes in the whole of the veterinary profession in the whole of the United Kingdom.

429. We have been told that globally the human/animal consumption comparison of antibiotics is about fifty fifty. Your figures tell us that in 1995—and you give it in pounds sterling?

(*Mr Cook*) Yes, that is right.

430. You tell us it is £2 million in humans and £12 million in animals, and here again, in the same thing, we have a similar comparison, 20 times as much. These two figures presumably can be compatible providing—and that is not unreasonable—that the cost of antibiotics given to animals is 20 times less than the cost of those given to humans?

(*Mr Cook*) It is not 20 times less, but it is true to say that the sort of uses that we have been talking about, such as growth promotion, are using elderly products which, as a result of that, have a low potency and so they tend to be used in larger quantities to get the same result, but they are also much less expensive than the most modern newly developed antibiotics in every walk of life.

431. So you would not disagree with the statement that in grammes as opposed to pounds the amounts given to animals and to humans are about comparable in the United Kingdom? The number is about the same, is it not, that is, the number of animals and the number of humans?

(*Mr Cook*) As far as human use is concerned, frankly, my Lord Chairman, we do not know. We would like to know. It is equally important to recognise, I think, the question of potency, and the potency of a gramme of a modern antibiotic can be several hundred times that of one of the most elderly original ones. All this needs to be taken into the calculation if you are trying to get a real measurement. It is a very difficult calculation.

432. Therefore, in view of what you have just said, Mr Cook, a comparison on the basis of the cost is not very realistic as a measurement of the amounts of antibiotics used?

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(Mr Cook) Not necessarily, my Lord Chairman, no, I would have to agree with that.

Baroness Masham of Ilton

433. Who is doing the monitoring?

(Mr Cook) Of what?

434. The monitoring of use?

(Mr Cook) My Lord Chairman, we run our own survey audit of animal medicine sales in this country

so we do have that information. As far as the human side is concerned I have no information. There are obviously Department of Health statistics, but we do not have them.

Chairman

435. We have still three questions which were not attended to and I wondered whether we could perhaps prevail upon you to give us a written answer to those?

(Mr Cook) Indeed, yes, my Lord Chairman.

Supplementary Memorandum by the National Office of Animal Health

Following our meeting with their Lordships on 25 November I am now in a position to respond to those listed questions which time prevented us from covering on the day. I have also taken the opportunity to update their Lordships on recent developments, to elaborate on some of the points previously covered and to comment on Dr Simmons' remarks on our evidence.

A OUTSTANDING QUESTIONS

A Question 2 (Part 2)

"We understand that the EU is conducting a monitoring programme, please tell us about this"

We promised further information:

There is indeed an international programme funded by the companies which produce feed additives, and a protocol (Copy attached) (*not printed*) which has been jointly drafted by FEFANA (the European Feed Additive Organisation) and the EU, together with the member states. The programme will monitor the resistance in *Enterococcus faecium* isolated from pigs and poultry in eight countries. It will be carried out on two consecutive years, to determine any changes in resistance which are occurring. This is a substantial study costing in the region of £600,000, but it represents a novel and important example of fruitful collaboration between industry, the EU and the member states.

A Question 3

How do you rate the evidence that animal use of apramycin may have induced resistance in *Salmonella typhimurium* DT 104 to Gentamycin?

As the company which supplies apramycin (Elanco) was not present, we offered to obtain more information. Their reply is as follows:

Resistance to apramycin is a very rare phenomenon. In surveys involving 10,000 organisms, (Veterinary Laboratories Agency, 1995) and Low *et al* (1997), the resistance rate was found to be 0.46 per cent.

There has been interest in the resistance mechanism because it offers an epidemiological marker to trace salmonella in the food chain.

However, after 15 years of usage of apramycin in animals in the UK, this ultra-low level of resistance is clearly of no clinical significance.

Attachments (*not printed*):

Salmonella in Livestock Production, VLA, 1995. Page 76, Table 43: *Salmonella typhimurium*: antimicrobial sensitivity monitoring 1989-95.

Antimicrobial resistance of *Salmonella enterica* Typhimurium DT 104 isolates and investigation of strains with transferable apramycin resistance. Epidemiol. Infect. (1997), 118, 97-103. Low, J C, Angus, M, Hopkins, G, Munro, D and Rankin, S C.

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A Question 9

What changes have occurred in the antibiotic resistance pattern of the gut flora of farm animals in recent years? Do you regard any of these changes as potentially significant for humans?

Firstly we would like to record that antibiotic resistance in general is not seen as a major problem in veterinary medicine in the UK. General study of the veterinary literature, plus informal discussions and general observation of the profession over the last decade indicate that it is seldom raised as a topic of concern. This observation is reinforced by both the Pharmacovigilance section of the Veterinary Medicines Directorate and by Dr Clifford Wray of the Veterinary Laboratories Agency, both of whom confirm that the problem is seldom reported to them.

There is however a shortage of data gathered in a consistent manner which would allow thorough evaluation of changes in gut flora over a period of years. Data such as there are suggest that there have been some changes in some cases, but that in general there appears to be a relatively stable situation. It is *not* the case that there are rapid and significant changes offering novel threats and dangers. The change which has attracted particular attention is the increase in fluoroquinolone resistance resulting especially from the prevalence of *Salmonella typhimurium* DT 104. However, this incidence in the UK is now apparently falling (C Wray personal communication), and this could well be followed by a drop in fluoroquinolone resistance in salmonella in the UK as is being experienced in the Netherlands, where the organism is also becoming less prevalent, (D Mevius, IDDL0 Meeting, Netherlands, 7 October 1997).

For Enrofloxacin and *E coli*

As already presented to VPC and ACMSF, regular monitoring has shown no change in the past five years in those countries where the product has been on the market for that time.

Overall our view is that what little change there has been is insignificant for humans.

A Question 10

Are there any changes in the regulatory and legislation framework you would like to see?

Our greatest concerns relate to developing trends, and changes which are taking place. In general we believe animal medicine regulation and use in the UK has been sensible, responsible and successful in providing a balance between necessary controls and availability. The very great success in reducing antibiotic residues in animal produce confirms this.

The Mutual Recognition Procedure of the EU should permit an approval in one state, e.g., the UK, to be taken as the basis of approval in other member states. In fact this is proving less than satisfactory, and we have examples of a product approved in the UK being subjected to review elsewhere to a degree that ignores the thorough and effective UK process.

The above Mutual Recognition Procedure also carries the risk of a country with a particular view on antibiotics, e.g., Sweden, having a distorting effect on the approval process throughout the EU.

Recently events such as the EU decision to ban avoparcin, against the advice of their own scientific committees, appear to herald a new approach where science can be abandoned in the face of political pressure, or to make obeisance to the "Precautionary Principle" (one wonders how many examples of technology in common use today would have survived if this ill judged "principle" had existed in the past—would, for example, penicillin, which kills guinea pigs, have survived such a precautionary approach?) We are equally concerned that, with the consequent quest for greater and greater safety, regulatory demands are reaching a level where development costs are so high that companies are deterred from investing in R&D for new, better, products—particularly for "niche" markets and minor species.

We do welcome the continuing drives to improve *traceability*, via record keeping and the encouragement of responsible use of medicines, as exemplified by the FEDESA document circulated at our meeting.

We would be particularly concerned if international initiatives to improve animals medicine controls world wide were adopted in UK and EU *on top* of our existing regulations, rather than the spotlight being focused on those parts of the world which are far behind us. Not only would this unnecessarily and unfairly burden UK farmers and vets, but it could distract attention from those countries where genuine improvement is needed.

A Question 11

What can you tell us about the use of antibiotics in aquaculture and horticulture?

Horticulture is outside our remit and expertise and, while we appreciate this principle has not deterred some of your other witnesses, we would prefer not to comment.

Similarly with aquaculture, we can only comment on the UK situation where, as indicated on page seven, item 10, of our written evidence, use of antibiotics has been greatly reduced over the past four years following

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the introduction of vaccines. Where antibiotics are used they are carefully selected and the licensing process includes having to conform to strict guidelines, especially with respect to environmental issues.

B FOLLOW-UP

While writing, may I comment on some other points that emerged during our meeting:

B1. *The WHO Berlin Conference*

Since we met the full report of that meeting has become available and it confirms our forecast that it was much more balanced than the WHO Press Releases, so much so that our published response to the press was able to be reasonably positive and I quote it in full:

The National Office of Animal Health has found much to support in the new report from the World Health Organisation on its meeting on the medical impact of the use of antimicrobials (antibiotics) in animals. But it could not approve of any decision to curtail animal antimicrobial use without the proper risk/benefit analysis that the report itself recommends. NOAH emphasises that the report is a commentary on the world situation—any national response should start with an appreciation of the controls already in place.

The experts, predominantly from the medical microbiological world, gathered in Berlin in October and confirmed that “antimicrobials are vital medicines for the treatment of bacterial infections in both humans and animals”. They also recognised they are “important for sustainable livestock production”. They believed there was “little doubt” that the bacterial resistance problems in medical practice were in general “. . . primarily related to the prescribing practices of health workers and to medication-taking practices of patients” and recommended close co-operation between all sectors involved in antibiotic use.

“We are pleased that this report acknowledges the benefits of antibiotics for animal but were disappointed to see the repetition of many controversial assertions,” said NOAH director Roger Cook. “We will need to examine the recommendations in detail to ascertain the real threat to animal welfare, farm economics and food prices if products are to be removed from the market for no good reason. The WHO missed the opportunity here to carry out the risk/benefit analysis that their own recommendations clearly require,” he said.

He agreed that these precious products should be used prudently in both animals and humans. “The report reviews the worldwide situation: happily many of its recommendations are anticipated by the controls that have been in place in the UK for many years. All UK animal medicines, including all antibiotics, have been evaluated and licensed by the UK competent authorities according to the Medicines Act 1968 (and subsequent EU legislation) which also regulates prescribing and distribution. Record keeping and residue monitoring are also part of EU law and the published UK results show the responsibility with which the UK veterinary profession and farmers use antibiotics” said Mr Cook.

The report also recommended the need for monitoring of resistance. NOAH endorses this recommendation, noting that this too has been anticipated in the EU, with a large surveillance programme already being undertaken by the feed additive companies with the European Commission. “There is a need to continually update what is really happening”, said Mr Cook. “Any decision on feed additives should await the result of this study, so that decisions can be based on fact rather than suspicion”.

The UK Government has a commitment to animal welfare and to consumers, said Mr Cook. “The proper and careful use of antibiotics in animals, both for therapy and as dietary enhancers, is crucial to both these.”

B2. *Alternatives to antibiotic growth promoters*

One point not made at our meeting is that if there are to be effective, predictable and safe replacements for these products then they are likely to fall within the scope of medicines or feed additive legislation and suffer the same burden of R&D/licensing costs as other medicines. This is an unfortunate but necessary imposition both to protect the public and the user and to ensure that they do not unfairly compete with those products *are* subject to these controls. It would be quite wrong to fall into the populist trap of thinking that because these “alternative” products are of herbal or other “natural” origin they are in some way “nicer” or “safer” than conventional products and so may be absolved from the rigour of licensing scrutiny and control.

B3. *The Swedish Experience*

Sweden has been presenting a very enviable “united front” with Government, veterinary and farming spokespersons travelling far and wide to publicise the virtues of their system. However, we have been aware, as indicated in our written and oral evidence, that things were less clear cut, with increased usage of “prescription

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only" and other antimicrobials replacing the banned products. Evidence of this inconsistency has now emerged from within Sweden itself, in a television "exposé". I attach a summary of the programme and we hope, in due course, to have a full translation of the Swedish transcript (*not printed*).

B4. *How Antimicrobial Growth Promoters Work*

Lord Phillip of Ellesmere quoted from a publication which says "in monogastric animals the mode of action is not clear but a number of theories have been advanced". I now understand he was quoting from the Veterinary Formulary, published by RPSGB. While we would not wish to quarrel with the authors of that book, Dr Bywater gave an explanation which showed that there is a great deal of understanding. A new FEDESA paper, to be published in the New Year, gives the following summary:

- "*They work by positively influencing the balance of intestinal micro-organisms, by promoting beneficial strains. This improves the absorption of the digestible constituents of feed and of water minimises the wasteful excretion of undigested nutrients*".

For some years the preferred industry term for those products has been "digestive enhancers" which more accurately summarises their action.

B5. *Dr Norman Simmons*

Following our own oral evidence the sub-committee heard from Dr Simmons. We were surprised to hear him asked to comment on our evidence, while we had no opportunity to comment on his. I hope we may now be allowed to redress the balance.

On page 30 of the transcript Dr Simmons gives a lengthy description of how he believes antibiotics are used in animals. His description is very confused and we were disappointed that he was not asked to support his assertions with evidence or fact, nor to substantiate his allegations. Without such probing, we trust that these remarks will be accepted as simple hearsay—inadmissible in either legal or scientific fora. It is *not* true, for example, that when "an animal falls ill" the vet immediately resorts to in-feed antibiotic treatment of the whole group: for many animals and diseases, individual treatment, usually by injection or intramammary infusion, is the norm.

While it is true that consumption is linked to hunger, animal nutrition is a much more precise science than Dr. Simmons' remarks and tone imply. It is also untrue to assert, as he does, that "within feed mills there is cross-contamination from one feed lot to another". While this may occur very occasionally it is regarded as unacceptable bad practice and there is a strict, legally required system of sampling, analysis and indeed, long-term sample retention. Their Lordships may come to call on the United Kingdom Agricultural Supply Trade Association (UKASTA), who represent the animal feed manufacturers, to explain the system of controls under which they operate.

It is also important to note the increasing use of in-water medication as a replacement for in-feed treatment—this can have a number of benefits: precision, timeliness, reduced risk of cross contamination, and the fact that sick animals are more likely to drink than feed.

Thus although Dr. Simmons' *anecdotal* comments may have been relevant in the distant past, the science of treating animals has moved on.

In fairness we should also welcome Dr. Simmons' recognition of the importance of continuing availability of antibiotics for veterinary use.

Dr Simmons asserts (page 33) "I do not think it (the UK veterinary sector) look, for resistance"—he gives no basis for this and we would refer you to our response to question 9. Their Lordships may also wish to obtain evidence from the Veterinary Laboratories Agency and others who are qualified to speak on this subject.

Also on page 33 Dr. Simmons states "we had great difficulty in finding out just how much antibiotics are given to animals". This is an odd remark, as Dr Simmons was present at the ACMSF sub committee when NOAH presented detailed figures—perhaps he had forgotten.

At the bottom of page 38 and on page 39 Dr Simmons hypothesises about the US situation—I have written to the Agricultural Attaché at the US Embassy and will write to you again when I have their response.

Dr. Simmons' presentation provides a fascinating summary of the opinions and perceptions held by the medical and microbiological professions of antibiotic use in animals, but that does not necessarily mean that he is correct.

B6. *To conclude*

We were very pleased to give evidence to their Lordships on this topical and controversial subject. However the Notice of this enquiry gives a very clear indication that it will *not* be looking into the question of antibiotic use in animals because this is being done by other groups. Because of this we understand that a number of

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veterinary and farming bodies, even MAFF itself, have been deterred from participating. However it is quite clear from their Lordships' remarks to us and from the evidence we have had the opportunity to see, that any medical witnesses have taken the opportunity to criticise veterinary and farming activities— often on the basis of anecdote and hearsay. We do urge the Sub-Committee, even at the risk of extending its timetable, to invite those who *do* have first hand knowledge of the control and use of antibiotics in animals (such as the veterinary profession and MAFF) to come and give evidence so that their Lordships' deliberations can be based on a factual and balanced review of the evidence from all parts of this debate.

Mr Roger R Cook

8 January 1998

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[Continued

Memorandum by Dr N A Simmons

INTRODUCTION

The Subcommittee of the House of Lords Select Committee on Science and Technology which is enquiring into the causes and consequences of resistance to antibiotics and other antimicrobial agents has invited me to give evidence on the subject of antibiotics in the food chain.

My biographical details are as follows: I was head of the Department of Clinical Bacteriology and Virology at Guy's Hospital at Guy's Hospital from 1972 to 1994. I gave up this post when Guy's and St Thomas' Hospital merged. However, I did not retire, but continued to pursue and expand my other professional interests which include food safety and foodborne microbial diseases. I am currently an Honorary as well as Emeritus Consultant in Microbiology to the Guy's and St Thomas' Hospital Trust; Hon Senior Lecturer in Microbiology at St. Bartholomew's and the Royal London School of Medicine and Dentistry; Director of Food Micro Ltd; Medical Adviser to Infection Management Ltd, and Consultant adviser to PPP Columbia Healthcare.

I have been a member of the Advisory Committee on the Microbiological Safety of Food (ACMSF) since 1990, and a member of the Advisory Committee on Novel Foods and Processes (ACNFP) since 1995. I have chaired two working groups of the ACMSF, one on VTEC (Report, 1995) and the other on Foodborne Viral Disease (Report in press).

I am a member of the Working Group of the ACMSF on Microbial Antibiotic Resistance (MARWG) which is assessing the risk to humans of antibiotic resistant organisms in the food chain. However, the views that are expressed here are my own and not necessarily those of either the ACMSF or the MARWG.

I have in the past been a member of Council of the British Society for Antimicrobial Chemotherapy, Chairman of the Association of Medical Microbiologists, President of the Hospital Consultants and Specialists Association and a member of the Health Services Advisory Committee of the Health and Safety Executive.

My Personal Interests are listed in the Annual report of the ACNFP, but I have no commercial or personal financial interests in this subject.

This document is in two parts. In the first part I discuss the use of antibiotics in animals; in the second part I introduce the subject of antibiotic resistance marker genes in genetically modified plants.

I. USE OF ANTIBIOTICS IN ANIMALS

When I use the term antibiotics in this document I will be referring to all antimicrobial therapeutic substances unless I specify otherwise. Generally speaking antibiotics may be given to food animals for one of three reasons: to treat an overtly infected animal, for prophylaxis and for growth promotion.

Prophylaxis

When animals are kept together and one of them develops an overt infection it is reasonable to assume that some of the others in the group may also be infected although they may not at the time exhibit symptoms of disease. In these circumstances antibiotics may be administered to all of the animals in the group to treat asymptomatic disease in some and prevent infection in others. Veterinarians refer to this practice as prophylaxis.

Growth Promotion

The administration of small subtherapeutic amounts of some antibiotics to some animals results in a more rapid growth. The mechanism by which growth promotion is brought about is not fully understood although a number of explanations have been put forward of which the following is an example. Antibiotics, it is said, may effect bacteria in the gut, improve the digestibility of the food and encourage growth of bacteria that reduce the subclinical effects of disease caused by pathogenic bacteria, thereby improving the food conversion efficiency. I find this explanation unconvincing, but the drugs unquestionably cause an increase in the growth rate.

Framework of Control

Antibiotics which are used for the treatment and prevention of animal diseases in the United Kingdom are available only on prescription from a veterinary surgeon. Growth promoters are regarded as feed additives and are available without prescription, but with restrictions on species, incorporation rates and supply. A list of the antibiotics, antibacterials and growth promoters now authorised for use in animals and fish in the UK, is given in Annex I. It has been reported that in 1998 the implementation of European Directive 70/524 may result in the deregulation of growth promoters.

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The Concerns

For more than 30 years doctors, microbiologists and veterinarians have expressed a concern that the use of antibiotics in food animals could result in the emergence of antibiotic resistance bacteria which could cause infections in man thus limiting the therapeutic options or even rendering the consequent infections untreatable. The greatest fears have surrounded the use of growth promoters which are given without prescription and which, because they are given in subtherapeutic doses are seen to be especially likely to select resistant organisms.

The Swann Committee and the Lamming Report

This worry, the growing incidence of antibiotic resistance in some salmonellas, the emergence of multiple antibiotic resistance and the discovery of transferable resistance led, in July 1968, to the setting up of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, which was also known as the *Swann Committee*. This Committee concluded that the administration of antibiotics, particularly at subtherapeutic levels posed hazards to human and animal health. It recommended that antibiotics used for growth promotion and available without prescription in animal feed should have little or no application in man and animals, that they should not impair the efficacy of prescribed therapeutic drugs through the development of resistant strains of the organism, and should be of economic value in livestock production in the UK. The Government accepted the Swann Committee's recommendations and a ban on the use of penicillin, oxytetracycline, and chlortetracycline for growth promotion was introduced.

In 1992 The Report of the Expert Group on 'Animal Feedingsuffs *The Lamming Report*') was published.

Paragraph 4.26 stated:

"*S. typhimurium* from cattle have become increasingly multiple antibiotic resistant; in 1981 15 per cent of such strains were multiple antibiotic resistant whereas in 1990 the figure was 66 per cent. Comparable figures for *S. typhimurium* were 2 per cent and 8 per cent. This suggests that the use of antibiotics for prophylaxis and therapy, at least in the cattle industry, has contributed to the emergence of multiresistant strains . . .

Paragraph 4.27 stated:

The use of a novel aminoglycoside apramycin in bovines has allowed for the first time an estimate to be made of antibiotic resistance due to antibiotic usage in animals. Although there is cross resistance between gentamicin (an antibiotic important in human medicine) and apramycin such cross resistance is not absolute and different mechanisms of resistance can be distinguished. We have received evidence that gentamicin resistance in *S. typhimurium* type 204c strains has arisen because of the use of apramycin in bovine husbandry and that seven of 26 (27 per cent) gentamicin resistant human clinical isolates of *E. coli* submitted for examination to the PHLS Reference Laboratory were also resistant to apramycin. Antibiotic resistance in *E. coli* is extremely important as the organism is a significant cause of human disease, particularly urinary tract infection. We have referred both issues, i.e., increasing multiple antibiotic resistance of salmonella and apramycin/gentamicin resistance, to the VPC for consideration. We have been told that they consider the prophylactic use of antibiotics with cross-resistance to those used in human medicine should be strongly discouraged. We welcome this view. We recommend that monitoring of antibiotic resistance of salmonella be continued and that routine monitoring of antibiotic resistance in human *E. coli* be established. The possible contribution of antibiotic usage in animals to antibiotic resistance in human isolates should, where feasible (i.e., as with apramycin), be assessed. We also recommend that not only should antibiotics giving cross resistance in human medicine not be used as growth promoters but that their prophylactic use in animals be reconsidered."

The Government of the day responded by saying that it would seek the advice of the Veterinary Products Committee and the Committee on the Safety of Medicines on the recommendation.

The Continuing Debate

The principles of the Swann Committee's recommendations have governed the use of antimicrobial products in animals since that time, but the argument about the extent to which the use of antibiotics in animals poses a risk to man has continued. A group at one extreme argues that the use in animals poses no significant risk to man. For it to do so, they say, would require the emergence of resistant bacteria in animals, the colonisation of man by the bacteria followed by human disease caused by them and the demonstration of consequent therapeutic failures. They say that this chain of events has never been conclusively demonstrated. They accept that antibiotic resistant bacteria appeared after the introduction of the use of oral antibiotics in animals, but that after an initial rise the proportion of resistant bacteria has remained virtually static or even declined, that few of the resistant bacteria found in man are derived from animals and that new effective antibiotics are available for the treatment of most resistant strains. They further argue that the use of antibiotics in farm animals has made a substantial

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contribution to the development of a highly efficient farming industry. In particular they point out that the housing or confinement of young animals is necessary in modern farming to provide shelter and aid effective husbandry. To deny farm animals antibiotics would not only be unethical, but also would severely damage the farming industry and substantially raise the price of food. In any case, they say, many of the antibiotic resistant bacteria found in animals were selected in man by the inappropriate use of the drugs and then transferred to the animals.

At the other end of the spectrum of opinion it is argued that because of selection pressure the use of antibiotics in animals inevitably gives rise to antibiotic resistant bacteria, that people and animals share a microbial ecology and that antibiotic resistant bacteria from animals unquestionably sometimes infect man. Furthermore, even those animal-derived resistant bacteria which do not themselves infect man provide a gene pool from which resistance may be transferred to human pathogens. The concerns of the people holding these views are enhanced by the recognition of the seriousness of the consequences of a continued rise in antibiotic resistance. Many of the advances in human medicine over the past 50 years have been made possible by the control of infection by antibiotics. If antibiotic resistance were to be the rule rather than the exception in normal human bacterial flora and the bacteria causing most human infections the effect would be catastrophic.

The concern about antibiotic resistance is reflected in the growing number of working groups examining the issues. In addition to the Subcommittee of the Science and Technology Committee of the House of Lords and the MARWG of the ACMSF, a working group of the Committee for Veterinary Medicinal Products (CVMP) is investigating the prevalence and effects of antimicrobial resistance in animals and its potential for transfer to man. In October this year in Berlin the World Health Organisation (Division of Emerging and Other Communicable Diseases and Surveillance and Control [EMC]) organised a seminar on the medical impact of antimicrobial drugs in food animals in Berlin. This was preceded by an electronic discussion with five hundred participants from all over the world. The summary of its conclusions is included as Annexe 2. Discussions on the subject have been held at several other international conferences.

SOME RECENT ISSUES

Although the Swann Committee recommended that antibiotics used as therapeutic agents in man should not be used as growth promoters in animals it did not make any recommendations for a restriction on the use of antibiotics belonging to the same family as an antibiotic used in man.

Many antibiotics have been found since the discovery and development of penicillin, but many are related to each other and they belong to a relatively few groups or families. Thus there are several penicillins, cephalosporins, tetracyclines, aminoglycosides, glycopeptides, etc. Bacteria which develop resistance to one member of a family of antibiotics frequently show an increased resistance to other antibiotics in the same group.

In recent years antibiotics which are related to antibiotics used in man have been used as growth promoters or for widespread prophylaxis. At the same time bacteria resistant to the agents used in man have emerged and it has been postulated that these organisms have acquired their resistance as a result of the use of the related substance in animals.

Avoparcin/vancomycin/teicoplanin resistant enterococci

Avoparcin, vancomycin and teicoplanin are members of the same group of antibiotics, the glycopeptides.

Avoparcin is used in animals and has been available as a feed additive in many countries (but not in the USA and Canada) since 1975. Like the other glycopeptides it is not absorbed from the gut. Depending upon the livestock 4 to 50 mg per kg is added to animal feed. Between 1975 and 1996 it was progressively used for feeding broiler chickens, turkeys, pigs, beef and dairy cattle, calves, sheep and goats. Its ergotropic (growth stimulating) effect is said to be due to a selective suppression of the Gram-positive bacterial gut flora including enterococci.

Vancomycin and teicoplanin are used in human medicine. Vancomycin has been available since 1956, but for many years it was little used because it was shown to have severe toxic effects. Subsequently, when methicillin resistant *Staphylococcus aureus* (MRSA) emerged as a significant pathogen vancomycin which was sometimes the only agent effective against it, was used more often. Teicoplanin is similar to vancomycin in most respects, but it is less toxic and more expensive. It became available in 1985. It too may be used to treat MRSA infections.

Both vancomycin and teicoplanin are also used to treat infections caused by enterococci resistant to the β -lactam antibiotics. Enterococci can develop resistance to the glycopeptides and most of the organisms resistant to one member of the group are resistant to them all. Consequently enterococci which become resistant to avoparcin are, for the most part, also resistant to vancomycin and teicoplanin. They may be referred to as glycopeptide resistant enterococci (GRE) or vancomycin resistant enterococci (VRE). In the United States in

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1993 8 per cent of the enterococci from nosocomial infections were glycopeptide resistant. In the UK, GRE are less common, but the number is growing.

In recent years there has been an increasing concern that the use of avoparcin in animals could result in the appearance of GRE which could effect man. The fears have been heightened by the demonstration that in the laboratory and possibly *in vivo* the resistance could be transferred to staphylococci. Due to these concerns bans on the use of avoparcin in animal feeds were imposed in Germany in January 1995 and Denmark in May 1995. (A ban had already been imposed in Sweden). As a long-term ban was seen to run counter to a European Directive the Scientific Committee on Animal Nutrition (SCAN) (DGVI, Brussels) was asked by the European Commission to examine the scientific evidence upon which the German and Danish decisions had been made. SCAN concluded that the evidence presented had not established avoparcin as a risk to human or animal health or the environment, that there was no need for the antibiotic to be withdrawn and that it was unnecessary for glycopeptide antibiotics to be reserved exclusively for human therapy. However, the SCAN decision was not uniformly accepted, particularly in Sweden, Germany and Denmark, and subsequently The Standing Committee, the committee with legal responsibility, after a further six months of debate differed from SCAN. Shortly after that the Commission banned avoparcin. The Commission's proposal to ban avoparcin which was presented to the Standing Committee in December, 1996, was approved with only the UK voting against and Belgium abstaining, and it took effect on 1 April 1997. I do not know the grounds upon which the UK decided to cast its vote against the proposal.

SCAN had also recommended that further studies should be undertaken and the commission has decided that a monitoring program should be initiated. A protocol has been developed jointly between FEFANA (The Federation of European Feed Additive and Nutritional Companies), the European Commission and member state experts co-opted by the Commission. In my view this expensive exercise is unlikely to resolve most of the critical issues.

The controversy, then, is likely to continue. GRE do appear when avoparcin is used and so far attempts to determine whether the strains are the same as those causing human infection by ribotyping and PGFE have been inconclusive.

Virginiamycin

The streptogramin antibiotics are naturally occurring compounds isolated from *Streptomyces pristinaspiralis* and the streptogramin family comprises several series of similar antibiotics including the pristinamycins and virginiamycins. Virginiamycin is a mixture of virginiamycin M (Streptogramin A type) and virginiamycin S (Streptogramin B type). It is used as a growth promoter in chickens, turkeys, swine and cattle. It is also used to prevent coccidiosis in chickens and turkeys and in swine for the treatment and control of swine dysentery. There is little information on impact of the use of streptogramin use in animals on antibiotic resistance. However, recently virginiamycin resistant enterococci have been found in turkey flocks fed virginiamycin. The importance of these observations is that quinupristin/dalfopristin, another streptogramin mixture, has recently completed phase 3 clinical studies in the United States and Europe and it was hoped that it would be suitable for the treatment of patients with GRE infections. The fear arises because virginiamycin use in animals may have already resulted in quinupristin/dalfopristin resistance.

The Quinolones

The new fluoroquinolones which became widely available at the beginning of the 1990s were a welcome and powerful addition to the range of antibacterial agents available for the treatment of infection in man and animals. The fluoroquinolone that is probably the one most used in man in the UK is ciprofloxacin. These agents are used for the treatment of Gram-negative and some Gram-positive infections, including those caused by MRSA. They have proved to be of particular value in the treatment of the enteric fevers caused by *S. typhi* and *S. paratyphi* A, B, C.

When they were first introduced it was said that their mode of action, the inhibition of bacterial DNA gyrase, would make the development of resistance in Gram-negative bacteria, including the campylobacters, almost impossible. Unfortunately, the prediction proved to be over-optimistic. Quinolone resistant campylobacters are occurring with increasing frequency. Campylobacters are the most commonly recognised foodborne pathogens in the UK. Now, in the Netherlands 30 to 35 per cent of isolates show enhanced resistance to nalidixic acid or ciprofloxacin. In Spain 29 to 50 per cent show enhanced resistance (Piddock WHO conference 1997) and in 1996, in a survey in Wales of 1113 *C. jejuni* from humans 12 per cent were resistant to ciprofloxacin (Rowe, Personal Communication). An important reservoir of *C. jejuni* and *C. coli* is poultry. The quinolone, enrofloxacin, is used in broiler chickens in the first week of life to reduce vaccination problems, or in the third or fourth week to reduce respiratory problems due to *E. coli* and there is a belief that the emergence of fluoroquinolone resistant campylobacters is a consequence of the use of the drugs in veterinary medicine. In the

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UK the use of enrofloxacin was not licensed until November 1993 and it was little used before January 1994. Unfortunately some of the poultry bought in the UK is imported from Europe and the birds may carry fluoroquinolone resistant campylobacters.

Salmonella typhimurium Definitive type 104 (DT104)

This organism was first reported in the UK in 1984 and is now the second most prevalent salmonella after *Salm. enteritidis* PT4 in man in England and Wales. The number of isolates referred to the PHLS Laboratory of Enteric Pathogens increased from 259 in 1990 to 3,837 in 1995. DT104 is a cause of illness in a wide range of food animals including cattle, sheep, pigs chickens and turkeys. Of particular importance is the increasing incidence of a multidrug resistant strain of DT104, R type ACSSuT (A,ampicillin; C,chloramphenicol; S,streptomycin; Su,sulphonamides; T,tetracyclines). In 1995 approximately 67 per cent of the strains from humans were penta-resistant and 27 per cent and 6 per cent of strains were additionally resistant to trimethoprim and ciprofloxacin respectively (Miller *et al.* WHO conference, 1997). In 1996, 14 per cent of 4,006 isolates from England and Wales were resistant to ciprofloxacin (Rowe, Personal Communication). Although antibiotic treatment is not indicated for the treatment of most cases of human salmonellosis, for some people, particularly the immunosuppressed, the elderly and the very young, it may be, and ciprofloxacin resistance in these patients is a serious event.

The rise in the number of reports of DT104 infections in man has coincided with reports of infection in cattle. In 1995 there were 1,197 incidents of *S. typhimurium* DT104 infection reported to MAFF and of these 78 per cent were in cattle; 995 of the strains were penta-resistant. I have no figures for the incidence of ciprofloxacin resistance in strains from cattle.

The appearance of ciprofloxacin resistance in strains from man coincided with the approval of enrofloxacin for veterinary use in the UK and some microbiologists feel strongly that it is a consequence of it.

In the United States the first FDA approval of a fluoroquinolone for use in food producing animals, broiler chickens and turkeys was sarafloxacin in 1995. The rise in the number of reports of ciprofloxacin resistant DT104 is now causing serious concern.

Fluoroquinolone resistant *E. coli* have also appeared and some seem to be associated with enrofloxacin usage in animals.

OPINION

As a member of the MARWG of the ACMSF, which is still taking evidence I must keep an open mind on most aspects of the problem, but on some of the basic issues I feel I can safely express an opinion now.

When antibiotics are used in man or animals selection pressures generally result in the emergence of resistant strains of bacteria. The rate of emergence of resistance differs with different antibiotics and the circumstances of exposure. Some of the resistant strains that appear in animals are capable of infecting man and some of them have caused infections in man. There is ample indirect evidence to support this conclusion, but unfortunately direct evidence is sparse as the appropriate controlled studies do not appear to have been done. For example, I have not seen any report comparing the incidence of bacteria resistant to avoparcin over a long period of time in a group of animals given avoparcin with the incidence in a group of animals not given the antibiotic. Nor have I seen similar studies with any of the other antibiotics used for growth promotion. I find this surprising as tests with each of the antibiotics would resolve at least some of the arguments. At this time the frequency with which transfer of bacteria from animals to man has occurred in the past and is likely to occur in the future is open to dispute.

In general, the more bacteria come into contact with antibiotics the more rapidly they develop resistance and, although the rate at which they do so differs with different antibiotics, the tendency is for bacteria to slowly become more resistant. Withdrawal of an agent from use may retard the process and even go some way towards restoring the *status quo ante*, but there is no evidence to show that it ever permanently succeeds in completely doing so and the reintroduction of the agent can result in the relatively rapid reappearance of resistance.

The antibiotic age then may be finite although it may last tens or, hopefully, hundreds of years and the development of resistance will be quicker with some antibiotics than others, but the more antibiotics are used (justifiably or unjustifiably) the shorter it is likely to be. In this respect, in the long term it will probably make no difference whether the antibiotics are used in man or animals because they both share a common ecology. If we wish antibiotics to remain as effective as possible for as long as possible we must use them as little as possible. Unfortunately, in animals and man in the past people have used antibiotics instead of alternatives considered to be more expensive in the short term. It is still the case.

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*The Specific issues***GRE**

GRE do emerge when glycopeptide antibiotics are used in animals. Whether these organisms have caused infections in man and if they do the extent to which they do so is open to dispute.

The Fluoroquinolones

Fluoroquinolone resistant bacteria now infect both man and animals. Some of the infections in man are probably caused by bacteria that acquired their resistance in animals, but the frequency with which this occurs or will occur is still uncertain.

Virginiamycin

The development of resistant enterococci is a worrying development. Again the paucity of research makes decisions on the appropriate action difficult.

II. THE USE OF ANTIBIOTIC RESISTANCE MARKER GENES IN PLANT GENETIC MODIFICATION

As a member of the Advisory Committee on Novel Foods and Processes I am aware of the problems posed by the use of antibiotic resistance markers in plant genetic modification. I will not cover the subject in detail, but I feel the subject is relevant to the deliberations of the Sub-Committee and therefore I have included a short section on it for the sake of completeness.

For those who wish to consider the subject in more detail two reports from the ACNFP may be of value (Report on the Use of Antibiotic Resistance Markers in Genetically Modified Food Organisms, 1994; The Use of Antibiotic Resistance Markers in Genetically Modified Plants for Human Food, 1996).

THE PROCESS

Plants may be genetically modified to give them properties that are considered to be desirable. For example, a plant may be made resistant to attack by insects or resistant to the action of a herbicide used for weed suppression. The process used to achieve this may be regarded as having two stages. In the first stage the genes of interest (trait genes) are prepared in a vector which is commonly *E. coli*. In the second stage, the gene construct containing the genes to be transferred is inserted into the plant. At neither stage is the process uniformly successful. Some vectors may carry the construct and others may not, some plants may be transformed and others may not. Antibiotic resistance genes may be used as selectable markers in both stages. In the first stage, the production of the construct, an antibiotic resistance marker gene, with bacterial regulatory sequences, may be closely associated with the trait gene on the construct. This allows those vectors which carry the trait gene to be selected by exposing them to the antibiotic. It is good practice to excise the marker gene before the construct is introduced into the plants as it is no longer needed, but this is not always done. In the second stage, an antibiotic resistance marker gene together with plant regulatory sequences is used to select those plants into which the trait gene has been introduced. Although the presence of the marker gene is necessary only immediately after the genetic modification procedure for the selection of the transformed cells the marker gene may remain and be expressed in the GM plant. There is a concern that the antibiotic resistance genes might be transferred back into bacteria and result in resistance to antibiotics used in man.

The most prominent debate concerned the production of a GM maize by Ciba-Geigy Ltd. The GM plant contained the trait gene derived from *Bacillus thuringiensis* conferring resistance to attack by the European corn borer and the *bla* gene together with bacterial regulatory sequence from *E. coli* which codes for resistance to β -lactam antibiotics, including ampicillin. The construct was introduced into immature plant embryos by micro projectile bombardment. The *bla* gene was used as a selective marker to indicate transformed *E. coli* during the development of the vector for the gene constructs and was not subsequently excised. Because the regulatory sequences are bacterial it cannot be expressed in the maize, but it can be expressed in bacteria. The maize is intended for processing and the ACNFP considered that the risk of genetic transfer to gut micro-organisms through the consumption of products made from processed grain could be discounted as processing would destroy any DNA present. However, the risk transfer of the *bla* gene to free living bacteria or to gut or rumen bacteria in animals fed unprocessed maize, however low, was considered unacceptable. The risk was regarded as small but finite and the ACNFP recommended that the gene should be excised before the GM maize could be grown for animal feed use. The European regulatory authorities, however, concluded that the size of the risk did not warrant a ban on the use of the unprocessed maize as animal feed.

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I was, of course, entirely in agreement with the ACNFP, and my concerns were enhanced by the fear that approval of the maize would set a precedent. Genes conferring resistance to other antibiotics can, and already have, been used as markers including npt II and npt III conferring resistance to some aminoglycosides and a gene conferring resistance to chloramphenicol.

ANNEX 1

LIST OF ANTIBACTERIALS, ANTIBIOTICS AND GROWTH PROMOTERS AUTHORISED FOR USE IN ANIMALS AND FISH IN THE UK

Antibacterial antibiotics—single

Active ingredient	Cattle	Sheep	Pigs	Poultry	Injection	Oral/ in feed	Intra mammary
Phenoxymethylpenicillin			✓			✓	
Procaine Penicillin	✓	✓	✓		✓		✓
Amoxycillin	✓	✓	✓	✓	✓	✓	
Ampicillin	✓	✓	✓		✓	✓	
Cefquinome	✓				✓		
Ceftiofur	✓		✓	✓	✓		
Cephalexin	✓	✓	✓		✓		
Cefoperazone	✓						✓
Cefuroxime	✓						✓
Cephacetrile sodium	✓						✓
Cloxacillin	✓	✓					✓
Cephalonim	✓						✓
Chlortetracycline	✓		✓	✓†		✓	
Oxytetracycline	✓	✓	✓	✓†	✓	✓	✓
Tetracycline HCl			✓	✓		✓	
Apramycin	✓	✓	✓	✓	✓	✓	
Framycetin Sulphate	✓		✓		✓	✓	
Neomycin Sulphate	✓	✓	✓	✓		✓	✓
Spectinomycin	✓	✓	✓		✓	✓	
Streptomycin Sulphate	✓	✓			✓		
Erythromycin	✓			✓		✓	✓
Lincomycin			✓		✓	✓	
Tiamulin Fumarate			✓		✓	✓	
Tilmicosin	✓		✓		✓	✓	
Tylosin	✓		✓	✓†	✓	✓	
Florfenicol	✓				✓		
Sulphadimidine	✓	✓	✓		✓	✓	
Sulphamethoxypyridazine	✓	✓			✓		
Enrofloxacin	✓		✓	✓†	✓	✓	
Danofloxacin mesylate	✓		✓	✓	✓		
Marbofloxacin	✓				✓	✓	

† Including turkeys.

Antibacterials/antibiotics—combinations

Active ingredient	Cattle	Sheep	Pigs	Poultry	Injection	Oral/ in feed	Intra mammary
Benzathine Penicillin/Procaine							
Penicillin	✓	✓	✓		✓		
Amoxycillin/Clavulanic acid	✓				✓	✓	✓
Dihydrostreptomycin/streptomycin	✓	✓			✓		
Baquiloprim/Sulphadimidine	✓		✓		✓	✓	
Trimethoprim/Sulphadiazine	✓	✓	✓	✓†	✓	✓	
Trimethoprim/Sulphadoxine	✓		✓		✓		
Trimethoprim/Sulphatroxazole	✓	✓	✓		✓	✓	
Trimethoprim/Sulphaquinoxaline				✓†		✓	
Trimethoprim/Sulphachlorpyridazine	✓		✓	✓		✓	
Chlortetracycline/Procaine							
Penicillin/Sulphadimidine			✓			✓	
Lincomycin/Spectinomycin			✓	✓		✓	
Neomycin/Streptomycin		✓				✓	✓
Tylosin/Sulphadimidine			✓			✓	
Procaine							
Penicillin/dihydrostreptomycin	✓	✓	✓		✓		✓
Procaine Penicillin/Neomycin	✓	✓	✓		✓		✓

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[Continued

Active ingredient	Cattle	Sheep	Pigs	Poultry	† Injection	Oral/ in feed	Intra mammary
Ampicillin/Cloxacillin	√						√
Chlortetracycline							
HCl/Dihydrostreptomycin	√						√
Chlortetracycline/dihydrostreptomycin/ neomycin sulphate	√						√
Dihydrostreptomycin/procaine penicillin	√						√

† Including turkeys

Antibacterials/antibiotics—Combinations

Active Ingredient	Cattle	Sheep	Pigs	Poultry	Injections	Oral/ in feed	Intra mammary
Framycetin/dihydrostreptomycin	√						√
Framycetin/Procaine Penicillin	√						√
Novobiocin/Procaine Penicillin	√						√
Benzyl Penicillin/Neomycin/Procaine Penicillin	√						√
Benzyl Penicillin/dihydrostreptomycin/nafcillin	√						√
Neomycin/Procaine Penicillin/Streptomycin	√						√
dihydrostreptomycin/neomycin/ novobiocin/procaine penicillin	√						√
dihydrostreptomycin/nafcillin/procaine penicillin	√						√
Neomycin/procaine penicillin	√						√

In feed growth promoters

Active ingredient	Cattle	Sheep	Species	Pigs	Poultry
Avilamycin				√	√
Avoparcin	√			√	√
Bacitracin Zinc	√			√	√
Bambermycin	√			√	√
Spiramycin	√			√	√
Tylosin phosphate				√	
Virginiamycin	√			√	√
Monensin sodium	√				
Salinomycin sodium				√	
Ardacin					√

Antibacterials/Antibiotics in Fish

Active ingredient	Administration in Feed
Amoxycillin	√
Trimethoprim/Sulphadiazine	√
Oxolinic Acid	√
Oxytetracycline	√

* Indicated in poultry with coccidiosis claims.

Active ingredient	Cattle	Sheep	Pigs	Poultry	† Injection	Oral/ in feed	Intra mammary
Olaquinox			√			√	

This active ingredient is authorised, but in view of the stringent warnings applied, is not currently marketed.

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ANNEX 2

ANTIBIOTIC USE IN FOOD-PRODUCING ANIMALS MUST BE CURTAILED TO PREVENT
INCREASED RESISTANCE IN HUMANS

Excessive use of antimicrobials, especially as growth promoters in animals destined for human consumption, presents a growing risk to human health and should be reduced, 70 health experts agreed Friday, 17 October, at a WHO meeting in Berlin, Germany.

The 70 participants from the fields of both human and animal health met from 13 to 17 October at the BgVV, the Bundesinstitut fuer Gesundheitlichen Verbraucherschutz und Veterinaermedizin in Berlin, to review the currently available knowledge on the hazards of the use of antibiotics in food animals. The BgVV is the WHO/FAO (Food and Agriculture Organisation) Collaborating Centre for Research and Training in Food Hygiene and Zoonoses.

Antimicrobials are vital medicines to treat human infections but their effectiveness is threatened by overuse and inappropriate use which contribute to the growing resistance of bacteria.

Public health consequences from the excessive use of antimicrobials in livestock production include the emergence of resistant microbes which can then be transferred to humans through the food chain. Resistant strains of four bacteria that cause disease in humans have been transmitted from animals to humans and shown to have consequences for human health. They are *Salmonella*, *Campylobacter*, *Enterococci*, and *E. coli*.

Direct evidence that antibiotic use in food-producing animals results in resistant salmonella infections in humans was presented at the meeting. "Although only a small proportion of infected people require antibiotic treatment, in these patients the options are severely limited by resistance," the experts concluded.

Experts cited the widespread use of fluoroquinolones, an important group of medical antibiotics, in food animals as a particularly important issue. Fluoroquinolone-resistant *Campylobacter* has been detected in foods and has also been associated with treatment failure in humans infected with this organism.

Healthy practices in animal husbandry reduce the need for antibiotics, the experts emphasised, and antibiotics should never be used as a substitute for adequate hygiene.

A decrease in use of antibiotics as growth promoters does not need to entail reduced productivity in animals and thereby economic losses to the food producer nor increased prices for consumer. It will also not necessarily result in the increased use of other drugs in the place of antibiotics, the experts said. Research on alternative methods to improve animal growth and feed efficiency was recommended.

Participants further agreed that there was a greater need for the monitoring of the presence or emergence of antibiotic-resistant bacteria in livestock and food of animal origin. Quantitative data should be collected, using standardised methods, from all points along the food chain. A WHO-sponsored meeting to discuss the establishment of monitoring systems for resistance in food animals took place at the BgVV on 17 and 18 October.

"We must be able to provide descriptive data on the extent and temporal trends of antibiotic susceptibility and facilitate the identification of resistance in humans, animals, and food of animal origin as it arises," said Dr Reiner Helmuth, from the BgVV, co-chairman of the meeting.

WHO will work to integrate resistance monitoring in food animals and food of animal origin with its ongoing programme of antimicrobial resistance monitoring of bacteria that cause human disease.

Co-ordination within and between countries must improve to ensure better preparedness and awareness of potential health problems. "Following the introduction of fluoroquinolones for use in poultry, there has been a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter* in poultry and infections in humans in many countries," the experts said. "The emergence of *Salmonella* with reduced susceptibility to fluoroquinolones in humans is another cause for particular concern."

To address the potential medical problems related to the user of fluoroquinolones in food animals, WHO envisages hosting a meeting in February at its Regional Office for the Americas (PAHO) in Washington, USA, on this topic.

WHO's Division of Emerging and other Communicable Diseases Surveillance and Control (EMC) will continue to foster international co-operation in the field of monitoring of bacterial resistance in hospitals and community settings, as well as in bacteria isolated from food animals and food of animal origin.

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Examination of witness

DR N A SIMMONS, Consultant Microbiologist, Guy's and St Thomas' Hospital Trust, member of the Advisory Committees on Novel Foods and Processes (ACNFP) and on the Microbiological Safety of Food (ACMSF), was called in and examined.

Chairman

436. Dr Simmons, thank you very much for coming before us this morning.

(Dr Simmons) If I may, my Lord Chairman, I want to make three or four points. First of all, I am not, as you know, my Lord Chairman, speaking on behalf of the committees on which I serve. I am not authorised to do that.

In respect of the first annex I have a revised document on the antibiotics that are available for use in animals which I got from the Veterinary Medicines Directorate recently through our secretariat, and I am happy to make that available to the Committee as it is more up to date.

There are two points that I want to make which I did not make in my evidence. The first is that I think that the easy part of this is to know where the problem is and what the potential problems are. The difficulty is in deciding what to do about it because the production and distribution of food in the modern world is a very complex subject. If you go into a supermarket and look at one area you might find food from 30 different countries and each country may have its own policy in terms of the use of antibiotics in its food producing industry.

The other point that I want to make is that my experience is that there is a misunderstanding on the two extreme sides of this argument. I do not think, on the one side, that doctors and to some extent the public understand how antibiotics are administered to animals. Their idea of the administration of medicine is nice little pills in precise doses that are given to individual people for a specified length of time at eight hourly intervals for one week, but when animals fall ill that is not how the antibiotics are administered. The vet may prescribe them or they may be food additives and they are produced in feed mills. Supposing an animal falls ill. The vet prescribes an antibiotic, the feed mill makes up the feed for that group of animals in accordance with the prescription and a lorry load of feed may be delivered to farm and put into the farm environment. The animals will come along and eat it really in accordance with how hungry they are. We are not talking about a precise science, it is a different thing, and within the feed mills there is cross-contamination from one feed lot to another, so it is not the same as in humans. It is not so precise.

The other thing is this, I have heard doctors say, why don't we ban it all, and stop giving antibiotics to

animals. Well, my Lord Chairman, if all we had to worry about was the emergence of antibiotic resistance perhaps we would, but we cannot just devastate the farming industry on no evidence. You could not do that.

On the other hand, I find a lack of appreciation by some people giving the other argument on just how dependent human medicine is on the use of antibiotics. If antibiotics did not work or if we reached a situation where they did not work human medicine would be put back 50 years. It would not just be that we would have to suffer scarlet fever, but a lot of the developments in modern medicine are dependent on the suppression of infection. I think that many of the anxieties among the medical profession arise from the fear of what it would be like without antibiotics. We are completely dependent upon them, perhaps over-dependent upon them.

437. Thank you, Dr Simmons. I think that is a useful way to lead into the **ACMSF working group on microbial antibiotic resistance** and what is the programme there and what is the other relevant current work that has gone on?

A. My Lord Chairman, if I may preface this by saying what the ACMSF is, it is an independent committee of experts which advises the ministers in various departments, principally the Ministry of Agriculture, Fisheries and Food, the Departments of Health, Scotland, Wales and Northern Ireland, on aspects of the microbiological safety of food. Things may be referred to the committee like the Salmonella in eggs issue or the committee may indulge in a bit of crystal ball gazing and decide for itself what it thinks are the emerging or possibly emerging issues which will be of importance. The committee then examines them in depth. It usually sets up a small working group with members of the committee and with outside experts, and then produces a report which goes to ministers with a series of recommendations which may or may not be accepted. Our crystal ball gazing is often quite fruitful: for example, we anticipated the VTEC problem.

We anticipated a problem with antibiotics or a possible problem with antibiotic resistant bacteria emerging from the use of antibiotics in the production of food and so a working group was set up. I think the stimulus was DT104, to which I refer in my evidence. We act in a way similar to your Lordships' Committee: we give everybody the opportunity to come and talk

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[Continued]

[Chairman *Contd*]

to us to express their views and to give us evidence. Some accept the invitations and some do not. We look at the scientific evidence to see what is and what is not available. Eventually we will make up our minds together on what we think should or should not be done. The antibiotics working group is about, I would guess, halfway through the work, although other people who have not served on so many committees think that we are a little farther advanced. We tend to encounter unexpected delays, my Lord Chairman.

The ACNFP is a different sort of committee. **The Advisory Committee on Novel Foods and Processes** advises ministers on whether new foods, that is, a food that has never been available before or one that has never been available in this country before, should be approved for release, and that includes genetically modified foods or products of genetically modified foods. I gave the most prominent example in my written evidence. Actually consideration of genetically modified food is not the biggest amount of work that we do. We do work with other new foods and processes as well, but it is certainly the most contentious area of our work. We have looked at the genetically modified area and we have to make decisions. We act within a European framework. In other words, in all the European Union countries there are similar groups advising their governments and any genetically modified substance may be submitted to any country for approval. Then, once a decision is made, the other countries have three months either to agree with it or to disagree with it. As long as we agree with it, it is easy, but if someone disagrees with it then it has to be resolved within the European context. We do not do research in the ACNFP.

438. If we may just come back to antimicrobial resistance, you have heard the NOAH presentation earlier this morning and their argument that resistance is at a relatively low level, that in the United Kingdom humans consume more antibiotics than animals, that the same is true in the third world and other points. Which of these arguments do you find most convincing?

A. My Lord Chairman, I think that they are exaggerated, if I may put it that way. Let us deal with them in turn, first, "that United Kingdom veterinary medicine encounters resistance at a relatively low level": I do not think that it looks for resistance. Most of the **research** that is done or that is presented to us is done to show that the antibiotics that are available are still effective. It does not search out resistance in herds or flocks or animals to which antibiotics have been administered. It is a big deficiency. Research is done for a different reason. It is usually based on wanting to show that "three blind mycin" is going to be effective if we carry on using it. It is not done to find out for example whether avoparcin resistant enterococci emerge in chickens if you give chickens avoparcin. Of course, my Lord Chairman, we are trying to find out the extent of the research that has been done.

Then number two, "that in the United Kingdom humans consume more antibiotics than animals": first—and I not speak for the Working Group—we had

great difficulty finding out just **how much antibiotics are given to animals**. I think that figures from NOAH, as the noble Lord pointed out, which are based on cost clearly do not tell you very much, and a lot of information is regarded as commercially sensitive. There is no central register of use. The records on farms are not that good, even where they are meant to be good, and even on the best farms they are not perfect. How much is given in humans is not easy to find out either, as you heard, but I do not think that that matters anyway. We are looking at animals in our committee and just because, for example, you were to find that antibiotics were abused in human medicine, that would not excuse any abuse in animal medicine. The fact is that we want them used properly in both areas.

Then next, "that diseases spread around the world via humans more than animals": well, they may well do, but you must remember how much food is spread around the world. It is enormous.

Then, "that the animal medicine industry, at least in the United Kingdom, is highly regulated and responsible": well, it is regulated, and if you regard it as responsible, it is a subjective evaluation. It may well be considered responsible.

Next, "that animal growth promoters and prophylactics offer benefits which outweigh any contribution to resistance": well, since we do not know how much resistance there is we don't know that. We do know that there are benefits. There are certainly commercial benefits, there is no question about that, but **farm practice** has evolved with the use of antibiotics, and the two are intimately linked. With a ban on antibiotics, the present system of farm management would not have evolved. That is what the Swedes found. They had to change. Whether or not that is right, I do not know. There are benefits and there are disadvantages. I think that it all depends on just what would happen if real resistance did emerge in the long term. Then the disadvantages would be great.

Next, "that therefore further restrictions on animal antibiotics would be unwarranted and even dangerous": well, we have not decided that yet in our committee and I would rather not express an opinion now because I would rather participate in the discussions in my own working group when that is decided, but I think that it will be a question for balanced judgment.

Lord Perry of Walton

439. We have had a lot of evidence from other people about the rate of resistance that is found in colonised people who are not ill. You are saying that there is no such evidence at all in animals?

A. Well, no, I think that there is evidence on a much smaller scale than in human medicine that when you give antibiotics to animals selective pressures result in the emergence of resistant organisms. I think that there is evidence, but it is not as great as there is in human medicine, first of all, because it is not always required and secondly, because the facilities are not always available for it to be done. However, I am sure

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[Continued]

[Lord Perry of Walton Contd]

that it does occur, but the fact that it has not been done enough results in this rather tedious argument that these resistant organisms just emerge and then the numbers stay at a relatively low level and never affect human beings, which I frankly do not believe.

Lord Dixon-Smith

440. I am just trying to get the balance, my Lord Chairman, because it seems to me that there is risk whatever you do. When you actually research new antibiotics for human use you do not start out by looking for resistance; resistance develops as a consequence of use and you find it subsequently.

A. The natural fact is that when antibiotics are used in man in hospitals huge numbers of antibiotic sensitivity tests are done with enthusiastic microbiologists looking to find the first resistant strains so that they can report them, and whenever they emerge they always report them. In the United States there are centralised computerised registers of sensitivity tests. You can look up the proportion of resistant strains of enterococci resistant to vancomycin, and you can find it just like that. (That is in the United States.) You cannot find that in respect of animals.

441. I accept that completely, my Lord Chairman. What I am saying is, you have to get the product to market—

A. Oh, yes.

442. —before you start, and if there were lots of resistant strains before you started it would not come on the market, would it?

A. Well, that is quite right. The only thing that I would say in respect of this to people who say, "It's not so bad", I am afraid is that I am a little bit gloomy about this. Two things: first, I know of no antibiotic which is as effective today as it was on the day that it was introduced. Increasing resistance is the natural sequence of events.

Chairman

443. Just on a point of clarification, Dr Simmons, when you talk about antibiotics in animal use are you differentiating between clinical use for disease and growth promoters, or are you putting them all together?

A. My Lord Chairman, I think that if we distance ourselves from the emotive aspects of this, the bacteria do not care why they come in contact with the antibiotics; they just know that someone is "shooting bullets at them"—(they do not even know that) and they get better at dodging them. The more that they are in contact with the antibiotics the greater the chance that resistance will occur. As far as the germs are concerned, if they are in humans, they will just dodge the bullets in humans and if they are in animals, they will dodge the bullets in animals. They do not cross from animals to man as easily as one might expect, but they do cross.

Lord Jenkin of Roding

444. I found that one of the most interesting parts of your paper was the description of the two arguments. In a sense, of course, it is a spectrum. You set that out

extremely clearly about the question of whether antibiotic resistance in animal flora poses a risk to man. In your last answer you have made it clear, as it were, which side of the line you come down on and that is interesting. For which infections do you think the evidence is the strongest? Is there any proven case of transfer of resistance in vivo from an animal pathogen to a human pathogen as opposed, of course, to the transfer simply of a bug like *Salmonella* which takes its resistance with it?

A. I am afraid that I do not quite understand the question.

445. If an animal pathogen has acquired a resistance, taking a related but different human pathogen, have you any evidence that the resistance from the one will appear in the other?

A. I am still not sure that I understand. I think that there are four groups of organisms, as the Berlin press release said, in which it is quite clear that resistance which has almost certainly been generated in animals may result in the resistant organisms coming to man and causing infections, *Salmonella*, *E.coli*, enterococci and campylobacter. As far as those are concerned in my view it is very likely, and in some cases quite sure, they have been transmitted from animals to man causing an infection which has had therapeutic difficulties in treating one because the organisms are resistant to antibiotics. There are certain specific animal pathogens for which antibiotics are given to animals which do not affect man and I do not know of any evidence to show that the gene cluster or the genes which are responsible for that resistance in that germ in those animals has gone into other microbes which then affect man. But as I grow older I have increasing admiration for the ability of bacteria to acquire genetic material, to learn and to transfer it one from the other and to learn how to avoid the effects of antibiotics.

446. We heard some fascinating evidence from the pharmaceutical industry about the work that is being done in unravelling the genomes of many of these common bacteria. Do you from your standpoint see that as an encouraging way ahead if one is going to overcome this problem of resistance?

A. Well, I do not know what the way ahead is to overcome it. I hope that that is a way ahead. It reminds me of the man who threw himself out of the Empire State Building and as he passed each window he said, "So far so good, so far so good": I know that we are out of the window, I just do not know how far we are above the ground!

Lord Walton of Detchant

447. My Lord Chairman, if DNA fingerprinting of an individual bacterial strain is possible in order to identify whether an organism responsible for human infection is derived from an animal source, why is such collaborative work not being done?

A. It is a good question though I cannot answer why—probably because the funds are not available and the skills are not available to do it, but work is being done. It is on a relatively small scale even round the world. It is particularly important, I think, in respect of

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[Continued]

[Lord Walton of Detchant *Contd*]

the avoparcin/vancomycin argument where some of the work, the strain typing, initially indicated that they were different, that is, that the enterococci in the animals were different from the ones in man. However, I heard some evidence quite recently which suggests that they may well be the same. I think that there are many, many different types and I think that we would like to see—I would like to see—a lot more of that work done.

Lord Dixon-Smith

448. Do you know of any convincing account of the rise of vancomycin resistant enterococcus in the United States of America in the absence of avoparcin?

A. Do I know of a convincing account? Well, convincing—I can think of some reasons, but I do not think that they have been proved. The United States is one of the biggest importers of food of any nation in the world. It does not have to use vancomycin or avoparcin on its own chickens; it can order chicken bits from Brazil and Venezuela in which all of these things are still used, and with the animal, with the meat, would come the germs on them. It is quite possible that the genes and even the bacteria came in or could have come in. It is not the only possible explanation but it could well be that the genes and the bacteria came in with their food and then with the increased amounts of use of vancomycin used in the United States, and it is used more there than in the United Kingdom, (though I expect its use is variable depending on which part of the USA you are in), that could have exerted a selective pressure resulting in the emergence of the resistant strains in that particular population. Or it may have been a result of vancomycin mechanisms itself that had an effect. There is nothing exclusive about the mechanisms that may have been involved; bacteria will respond however they think best, so both mechanisms may have been used, or all three mechanisms, the gene, the bacteria, the selective pressure of the vancomycin.

Then the other thing which people have shown, my Lord Chairman, is that in the hospitals, (although it is not part of the food issue), it is the use of the cephalosporins which results in the emergence of the vancomycin resistant strains, probably because the vancomycin resistance gene cluster and the gene which are responsible for the emergence of the cephalosporin resistance are linked together so that one antibiotic may result in the emergence of strains resistant to other antibiotics. So that all these possibilities exist. Just to say that avoparcin has never been used in America and therefore it cannot be the avoparcin that was responsible for the emergence of the enterococci is not necessarily true. They just illustrate that in the emergence of resistant bacteria, the international dimension that I referred to right at the beginning of my statement is important, my Lord Chairman.

449. Is the international initiative trying to bring some order into this chaotic system sufficient or is it rather lacking, do you think?

A. It is growing. I think that the World Health Organization is showing a greater interest now. There was the Berlin conference which I mentioned. I could not give you the final report of that conference because

it was not available when I gave you my written paper, and so I gave you the press report. The final report is due shortly. There is another conference early next year on the use of the fluoroquinolones in animals and there are a lot of nervous people walking about wondering whether there will be an international recommendation for a restriction on the use of fluoroquinolones in animals; but that is something that is going to be tackled internationally. Your experience of international agreements is greater than my own, my Lord Chairman, but I think that to get the whole world to agree to anything would be rather difficult, but we are doing our best to do something in Europe.

I am concerned, about the suggestion that has been put forward that the regulations in this country which were based on the conclusions of the Swann report will be abandoned next year, and I think that I can say that we in our working group have asked to have some comments on that, we have asked to have some legal assessment of what the likelihood is, because that would be a very retrograde step. Many other countries, even if they did not say so, use the Swann recommendations as a basis for the use of growth promoters in animals so that if they were to be abandoned it would be really very unfortunate, but I do not want to base my comments on whether it will or will not happen on the evidence that I have received so far. I would like to have some word from the lawyers.

Baroness Platt of Writtle

450. You mention the possibility that animal use of antibiotics in the same family as clinical antibiotics but not sufficiently close to be prohibited under the Medicines Act may none the less give rise to cross resistance. Can you point to any particular cases where there is "clear and present danger"?

A. My Lord Chairman, I think that the two areas, of course, are the fluoroquinolones where the fluoroquinolones used in animals, for example enrofloxacin, are different from the ones used in man, (sarafloxacin, in the United States), and avoparcin is another area where there is a big worry.

I think that on the subject of fluoroquinolones DT104 has provided a great stimulus for the concern over the whole area. I have given figures for resistance in my written evidence. There is a deep concern. The people who are doing surveys on this do link the emergence of ciprofloxacin resistant *Salmonellas* of all sorts with the greater use of the fluoroquinolones in animals. That is very worrying, particularly for people who have managed to treat patients with severe paratyphoid and typhoid. I know that these are relatively rare diseases, but once you have used fluoroquinolones the thought that one day you will not be able to use them again really is terrifying. That is why I say you cannot ease anxieties based on your own experience.

451. You mention virginiamycin which was used in animals before human use was contemplated by which time resistance had already emerged. Is there a case for restricting animal use of any antibiotic for fear of compromising human medicine in unforeseeable ways? I should like to add that I turned over to the end of your

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DR N A SIMMONS

[Continued]

[Baroness Platt of Writtle *Contd*]

evidence to what I thought was a fascinating statement of principle. You say, "If we wish antibiotics to remain as effective as possible for as long as possible we must use them as little as possible." That is a very sweeping statement.

A. Yes, but it is the only way that we can approach it. It is no good putting the umbrella away for a rainy day and then letting people die now. We have to use antibiotics while they give us an advantage, but we should not squander them either in human medicine or in animal medicine. Someone came to our committee—it may even be someone who has come here to your Committee today—and started telling us about human medicine and how doctors abuse antibiotics, and I said, "You needn't knock the doctors, we give them sufficient criticism for abusing antibiotics, but that has got nothing to do with the present argument". I think that there is a case for slowly winding down antibiotic use and getting them less and less used. As I said at the beginning, antibiotic resistance is not the only problem in this world. The farming industry has to be maintained, and the price of food has to be maintained. We ought to work out where we are going and then we ought to work out the most advantageous and best way of getting there. I know that it is a sweeping statement, but I would not suggest that you could ban the use of antibiotics in animals, as I have heard some doctors say. That would just devastate farming and it would give all our competitors the opportunity to produce all our food; and the ability to produce food containing antibiotic resistant bacteria at a cheaper cost than us and export them to us. We would get the worst of all worlds—no farming industry and resistant bacteria, and that would do no good. We have to look at this in a balanced way. Nevertheless the object for everybody is to get slower development of resistance. The fact is—and I do not want to overstate, I have been as practical as I could—that antibiotics are a fantastic gift. To waste them just to get smaller amounts of animal faeces seems to me to be a mistake.

Chairman

452. Dr Simmons, as you may know, some members of the Committee were in the United States only last week. We met John McGowan, whom I am sure you know. He made what I consider to be a very pertinent comment. He said: a lot more drives antimicrobial resistance than the overuse of antibiotics. Would you agree with that?

A. Well, my Lord Chairman, I think that is very deep. I would need notice of that. Yes, I think, a lot more does drive it than the overuse of antibiotics. I think it is the use of it, not the overuse. Even if antibiotics are justifiably used resistance is likely to occur. It is not a question of overuse; it is use. If they are not used at all we will have plenty of sensitive organisms and a lot more dead people and that will not do anyone any good.

Lord Rea

453. What about sub-therapeutic use?

A. I must say that I found in some of the arguments that are put to us, the idea that if you use very little

antibiotics resistance will not emerge is naive. It is not true. The less you use, the sub-therapeutics amounts, are the ones which are the most likely to result in the emergence of resistant bacteria.

454. That is what I wanted you to say!

A. That is quite clear. Thirty years ago when I was a lad that is the way that you made resistant bacteria in the laboratory: you exposed them to increasing amounts, very small amounts, of antibiotics, then you could actually get resistant bacteria. They may not be stable, but sometimes something seems to click in the genetic makeup of the organism and then it becomes stable, and that is what the danger is, because I think that when you stop using the antibiotics, although the incidence of resistance does decline, it does not always go back to where it was before you started and then when you re-expose them to the antibiotics the emergence of resistance is that much quicker—they get used to it.

Lord Walton of Detchant

455. And when you use the word stable there, you mean stable resistance?

A. Yes—I mean, I did work with staphylococci, making them resistant to penicillin.

456. Let us just ask you about the World Health Organization meeting in Berlin. It recommended improved monitoring of resistant bacteria in livestock and food. Can you envisage a surveillance regime which would be both practical and really useful? What are the key questions? Who would you expect to bear the cost? What other research in this area would you most like to see and who would fund it?

A. I would like to see more basic research. I think we just ought to know whether resistant bacteria emerge when you give the antibiotics to the animals. I would like them characterised and I would like the strain typing done. Who would fund it? Well, there are only two sources of funding: one is the taxpayer and the other is the customer. If the industry does it they will put their charges up and then the customer will have to pay, so one way or another we are all going to have to pay for it. I think that in the first instance it will have to be funded by the taxpayer, but both the industry and the taxpayer will have to fund it.

457. When you say taxpayer you mean the research councils?

A. The Ministry of Agriculture, Fisheries and Food.

458. And other government departments?

A. And other departments, yes, there is research going on.

459. And what about the surveillance? Can you think of a practical and useful surveillance system?

A. Yes, I am not making a research grant application, but I am sure that I can think of one that would pass my test.

460. Perhaps you could define it for us in subsequent correspondence?

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DR N A SIMMONS

[Continued]

[Lord Walton of Detchant *Contd*]

A. I am sure we will define it in the ACMSF working group, my Lord Chairman.

Lord Perry of Walton

461. We have heard from a lot of sources about the use of antibiotics in fish farming. Do you think that there is a danger of getting the passage of resistant strains from fish?

A. There would be. We have had some evidence in our working group from Dr Alderman and Dr Hastings about the use of antibiotics in fish. If we had had this meeting in 1990 I would have been very depressed, but in United Kingdom fish farming the amount of antibiotics used appears to be declining and it appears to have declined in the past five years substantially. The reason that we were given for that is that the development of vaccines became more commercially viable. The number of antibiotics and the amount in which they are used has gone down in the United Kingdom. In other parts of the world that is not so. It has gone down, we think, in Norway and in some other parts of Europe, particularly in the production of salmon. Antibiotics were used in very large amounts for the treatment of furunculosis. The biggest aquaculture industry is in Asia, where there is a very substantial use of antibiotics. As a sideline, in the paper that we were given by Dr Alderman and Dr Hastings, there was a mention of antibiotic resistance in bacteria in ornamental fish, which is a very considerable problem. Apparently antibiotics are used in relatively large amounts in ornamental fish. It was not part of the work of our working group, but it was just an appendage, as you might say, and it might interest you to have that, my Lord Chairman. I am sure that the people who presented a paper to us having prepared it would be happy to let the Committee have it.

462. It is very difficult to know quite how it would be transmitted by ornamental fish.

A. People hold ornamental fish, and terrapins, they put their hands in the water and all sorts of things like that. We know that *Salmonellas* in terrapins cause quite severe disease in man and they are now coming out as resistant.

Chairman

463. What about horticulture and the use of antibiotic sprays to control certain diseases of fruit?

A. Streptomycin on apples and things like that you mean?

464. Yes?

A. I would say that we should frown on it, and I think that it is frowned on in the United States. Very much so. We do not want to spray these things around, it is just unnecessary.

Baroness Masham of Ilton

465. If we may just get back to the fish, in Norway they put a lot of antibiotics into the water in rivers and then it got into the drinking water, we were told in the

States, and that is why they stopped it. In fish farming are they put in for growth promotion or for healthy fish?

A. No. Because the fish are being farmed in close proximity to each other they develop diseases which are either uncommon in the wild and more common in the farmed fish or more severe and that is why they are using them. They administer them in baths or in pellets.

Lord Winston

466. And stress in the fish?

A. That is mentioned as a cause. I am not quite sure how you measure stress in a fish. It would be quite an interesting exercise in a research application!

Chairman

467. May we go on now to the ban on avoparcin. Following the European Union ban on avoparcin what growth promoters are next in line for critical scrutiny do you think?

A. There are whispers about the virginiamycin problem. I am not sure exactly how much growth promoters are used nowadays and I think that there is a great pressure now for people to use alternatives. In the veterinary community people are saying that there are alternatives to growth promoters, and I think that they will emerge. I cannot tell you any other specific ones. I have not looked at all the ones to see which ones they might be. I think the other thing to remember about the fluoroquinolones, my Lord Chairman, is that they are only licensed for the treatment of disease, but they are used for, if I may put it this way, mass medication. They are used in vaccine programmes and they are used in very young animals so that although they are not used for growth promotion, and the amounts used are greater, mass treatment is causing concern. However, that does not answer your question. I cannot answer it.

Baroness McFarlane of Llandaff

468. To what extent do you think that the problem would be solved if the recommendations of the Pennington Committee for a food standards agency are fully implemented?

A. I do not think that it is related in any way to this problem. I think there are many aspects to the subject of a food standards agency, but it is not related to the prevention of antibiotic resistance. I think that it will take a long time for it to do a lot of good.

Lord Porter of Luddenham

469. If I may move to a different field, my Lord Chairman, the plant field, and particularly **genetically modified plants**, you expressed concern about the possible dangers of antibiotic resistance marker genes. You fear that approval of unprocessed Ciba-Geigy maize—which I think is used in vast amounts now, because I saw a figure that it is about half in the United States—by the European Union may have set a precedent. Are other similar applications in the pipeline?

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DR N A SIMMONS

[Continued]

[Lord Porter of Luddenham *Contd*]

A. If I may go back first to how much is used, I think the amount of Ciba-Geigy maize that is used is not very great. The amount of genetically modified maize I think is considerable, but in Europe it is not. It may be quite great in the United States.

470. I heard a figure of 50 per cent in the United States.

A. It could well be. I do have to look at applications through the committee for genetically modified products and different antibiotic resistance markers keep appearing. I have mentioned three here. And people tend to ring me up and say, "If we were to make something with, for example, vancomycin resistance as a marker gene, would that be a problem?", and I say, "Well, yes, it would!". I think people are using a number of marker genes and I would hope they could progress to not using any. It is such a waste and in the long term it is unnecessary. Commercially, having developed a product, to tell people to go back and redevelop it without a marker gene is just very unpopular. I was personally worried that the maize would create a precedent, and I think that it has. And I fear that whenever we stop something for the same reason, (because it has an antibiotic resistance marker gene and a bacterial promoter and we are worried about it) it will be challenged in Europe and what will then emerge I do not know. The Americans are not worried about it, as you may have learnt in the States, my Lord Chairman. There is a tremendous difference in national attitudes to all these problems.

471. Is continuing research being done on the bacteria to detect the spread of the gene?

A. Yes, my Lord Chairman. The ACNFP does not do research, but I am aware that MAFF has actually commissioned some research. I am not in a position to say what it is, but I am sure that if you were to ask the secretariat of the committee they could show you some of the research that has been commissioned and that we are doing our best to find that out.

Lord Perry of Walton

472. You give us an unqualified statement, a strong statement, that use of antibiotics should be reduced in all of these areas. Would you like to translate that into control?

A. In human medicine there has been tremendous abuse of antibiotics as well. We call it abuse, but I think that is a bit pejorative. I think that people have seen antibiotics as an alternative to building a new operating theatre or having a better infection control policy.

473. We heard in the States about the use of vancomycin.

A. Yes, and I think that all these things should be controlled. In other words, we should take steps, and they will not be simple steps, to reduce usage, for

example, better education, if people are educable. And all of these things should be done in human medicine as well. I had better not go into human medicine. However, I think in respect of the use in animals too we should try to get better use of antibiotics. I have given it some thought and I only wish that we could find a better way of administering antibiotics to the animals. I think that it needs some lateral thinking, some greater research. Could we, instead of giving a great lorry load of animal feed containing tetracycline or suchlike, think of a better way of administering them? I think the problem is that the whole psychology in the animal world is different. A long time ahead perhaps we may get to that, but the only way ahead now is to look at alternatives to the growth promoters, to develop them, and persuade people that they are economically viable and that the dangers of using antibiotics instead are high. In Sweden, where I think they were driven on by a number of people who were really concerned about this, they managed to make the change, but it has resulted in a change in their industry and it would be a much bigger change in our industry. Our farming industry is much bigger than the Swedish one and we are bound in with the European Union.

Chairman

474. Dr Simmons, in answering a question by Baroness McFarlane you said that a food standards agency probably would not have much effect?

A. No.

475. But there is another area that I do not think we have yet touched on. That is the major food retailers in the country, the **supermarkets**, and they have increasing numbers of quality controls for all sorts of things. In the United States we heard that some supermarket chains were beginning to apply controls on the use of antibiotics in animal feed and milk, although with pasteurisation that does not come into it. It may well be through private quality control programmes such as that that there is quality control that would not be able to be exercised through any official agency. Would you like to comment on that?

A. My Lord Chairman, they are getting interested in it. As you know, 40 per cent of the food sold in the United Kingdom is sold to four major supermarket chains and if they decide on something they can exert considerable pressure. I think that if they are convinced of the need, they will move towards it, but it will be driven by the consumer as well. The supermarket asks, "will it sell?" The farmer says, "Will it make me be able to produce cheaper animals and make my life easier". Therefore, at each stage of the food production chain people ask different questions, but certainly if the consumers and the supermarkets before them decide, shall we say, that they do not want a particular antibiotic used in the production of food, they will be able to exert considerable pressure.

476. Dr Simmons, thank you very much indeed.

A. It was a pleasure, my Lord Chairman.

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[Continued

Additional material from Dr Simmons

Use of antibiotics for therapy in the UK

Active ingredient	Cattle	Sheep	Pigs	Poultry	Cats and Dogs	Other species	First licence issued	Likely route of administration (oral/injection/topical)	Individual/flock treatment	Used in human medicine
Phenoxyethyl penicillin			x				21.6.93	Oral	Flock	yes
Procaine Penicillin	x	x	x		x	Horses	22.12.71	Injection	Individual	yes
Amoxycillin	x	x	x	x	x	Salmon Ducks Pigeons	6.2.84	Injection Oral	Both	yes
Ampicillin	x	x	x		x	Horses	11.6.74	Injection Oral	Both	yes
Cefquinome	x						8.11.93	Injection	Individual	no
Ceftiofur	x		x	x		Horses	30.12.91	Injection	Individual	no
Cephalexin	x	x	x		x		16.7.91	Injection Oral	Individual	yes
Cefoperazone	x						5.6.85	Topical	Individual	no
Cefuroxime	x						7.4.87	Injection	Individual	yes
Cephacetrile Sodium	x						20.10.85	Topical	Individual	no
Cloxacillin	x	x			x	Horses	11.6.74	Topical	Individual	yes
Cephalonium	x				x		1.1.92	Topical	Individual	no
Chlortetracycline	x		x	x ¹	x	Ducks	29.3.85	Oral	Both	yes
Oxytetracycline	x	x	x	x	x	Horses Deer Salmon Trout Fish	22.12.71	Injection Oral	Both	yes
Tetracycline HCl	x	x	x	x	x		22.12.71	Oral	Both	yes
Apramycin	x	x	x	x		Salmon Trout	2.9.92	Injection Oral	Both	no
Framycetin Sulphate	x		x		x		24.9.74	Injection	Individual	yes
Neomycin Sulphate	x	x	x	x	x	Horses	8.11.73	Oral	Both	yes
Spectinomycin	x	x	x	x		Trout	15.10.92	Injection Oral	Both	yes
Streptomycin Sulphate	x	x	x		x	Horses Goats	6.8.73	Injection	Individual	yes
Erythromycin	x			x			29.3.85	Oral	Flock	yes
Lincomycin	x		x	x	x	Trout	14.5.90	Injection Oral	Both	yes
Tiamulin (Fumarate)			x				25.5.85	Injection Oral	Both	no
Tilmicosin	x	x	x				14.9.88	Injection	Individual	no
Tylosin	x		x	x ¹	x		31.8.72	Injection Oral	Both	no
Florfenicol	x						13.12.94	Injection	Individual	no
Sulphadimidine	x	x	x				6.6.73	Injection Oral	Both	yes
Sulphamethoxypyridazine	x	x					6.1.89	Injection	Individual	no
Enrofloxacin	x		x	x ¹	x		6.2.91	Injection Oral	Both	no
Spiramycin	x				x		1.9.72	Injection Oral	Individual	no
Enrofloxacin	x		x	x ¹	x		6.2.91	Injection Oral	Both	no
Danofloxacin mesylate	x			x			22.1.93	Injection	Individual	no
Marbofloxacin	x		x		x		10.2.95	Oral	Flock	no
Benzyl Penicillin/ Dihydrostreptomycin/ Nafcillin	x						26.8.76	Topical	Individual	related ²
Neomycin/Procaine	x						29.3.85	Topical	Individual	related ²
Penicillin Streptomycin										
Dihydrostreptomycin/ Neomycin/Novobiocin/ Procaine Penicillin	x						29.3.85	Topical	Individual	related ²
Spiramycin	x	x	x	x	x	Goats	1.9.72	Oral	Flock	no
Neomycin/ Procaine	x	x	x		x	Horses	24.7.85	Topical	Individual	related ²
Penicillin										
Tylosin Phosphate			x				7.9.79	Oral	Flock	no
Chloramphenicol					x	Horses	26.8.86	Injection Oral	Both	Yes
Oxolinic Acid								Topical		
Oxytetracycline	x	x	x		x	Fish Fish Deer Birds	27.7.83 17.9.93	Oral Oral	Flock Flock	no yes
Benzathine Penicillin/ Procaine Penicillin	x	x	x		x	Horses	4.4.85	Injection	Individual	related ²

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[Continued]

Active ingredient	Cattle	Sheep	Pigs	Poultry	Cats and Dogs	Other species	First licence issued	Likely route of administration (oral/injection/topical)	Individual/flock treatment	Used in human medicine
Amoxycillin/Clavulanic Acid					x		20.8.90	Oral	Individual	yes
Dihydrostreptomycin/Streptomycin	x	x	x				1.9.82	Injection	Individual	related ²
Baquiloprim/Sulphadimidine	x		x				20.11.91	Injection	Both	related ²
Trimethoprim/Sulphadiazine	x	x	x	x ¹	x	Horses Salmon	17.12.86	Injection	Both	yes
Trimethoprim/Sulfadoxine	x		x		Dogs only	Horses	23.4.90	Injection	Individual	related ²
Trimethoprim/Sulfatroxazole	x	x	x		Dogs only		22.11.85	Injection	Individual	related ²
Trimethoprim/Sulphaquinoxaline				x ¹			1.12.89	Oral	Flock	related ²
Trimethoprim/Sulphachlorpyridazine	x		x	x			13.11.88	Oral	Flock	related ²
Chlortetracycline/Procaine			x				31.8.90	Oral	Flock	related ²
Penicillin/Sulphadimidine										
Lincomycin/Spectinomycin			x	x			22.2.93	Oral	Flock	related ²
Neomycin/Streptomycin		x					20.10.83	Oral	Individual	related ²
Tylosin/Sulphadimidine			x				15.8.88	Oral	Flock	related ²
Procaine Penicillin/Dihydrostreptomycin	x	x	x		x	Horses	29.3.85	Injection	Individual	related ²
Ampicillin/Cloxacillin	x						11.6.74	Topical	Individual	yes
Chlortetracycline/Dihydrostreptomycin	x						29.3.85	Topical	Individual	related ²
Neomycin Sulphate										
Novobiocin/Procaine Penicillin	x						23.3.79	Topical	Individual	related ²
Clindamycin					x		9.6.89	Oral	Individual	yes
Hydrochloride										
Baquiloprim/Sulphadimethoxine					x		27.9.91	Injection	Individual	related ²
Procaine Penicillin/Sodium Nafcillin	x						26.8.76	Topical	Individual	related ²
Gentamicin					x	Rabbits	24.1.85	Injection	Individual	yes
Cefadroxil					x		20.4.90	Topical	Individual	yes
Procaine Penicillin/Streptomycin	x						29.3.85	Injection	Individual	related ²
Sulphaquinoxaline				x			30.6.89	Oral	Flock	no
Benzyl Penicillin						Horses	5.12.90	Injection	Individual	yes
Benzyl Penicillin/Streptomycin	x						22.7.92	Topical	Individual	related ²
Amikacin						Horses	20.4.90	Topical	Individual	yes
Doxycycline					x	Pigeons Caged birds	27.6.91	Oral	Both	yes
Framycetin/Dihydrostreptomycin	x						29.3.85	Injection	Individual	related ²

¹ Including turkeys.² Where there are combinations of active ingredients and one or more of them are used in human medicine this is indicated by the word "related".*Feed additives (oral use only)*

Active ingredient	Cattle	Sheep	Pigs	Poultry	Other species	First licence issued	Volume used ¹	Also therapeutic/Prophylactic use	Used in human medicine
Avilamycin			x	x		26.8.86		no	no
Bacitracin Zinc	x	x	x	x	Small animals Rabbits Mink	1.9.72		no	yes
Spiramycin	x	x	x	x	Goats Animals bred for fur	1.9.72		yes	no
Tylosin Phosphate			x			7.9.79		yes	no
Virginiamycin	x		x	x		1.2.83		no	no

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[Continued

Active ingredient	Cattle	Sheep	Pigs	Poultry	Other species	First licence issued	Volume used ¹	Also therapeutic/ Prophylactic use	Used in human medicine
Monensin Sodium	x			² x		16.11.73		no	no
Salinomycin Sodium			x	² x		11.1.83		no	no
Olaquinox			x			20.3.86		no	no
Flavophospholipol	x		x	x	Rabbits	29.4.87		no	no

¹ Including turkeys.² Indicated in poultry with coccidiosis claims.³ Information currently unavailable.

*UK animal medicine market
1996 product types*

	Per cent sales value
Endoparasiticides	23.4
Vaccines	22.1
Ectoparasiticides—farm	5.5
Ectoparasiticides—pet	6.9
Antiseptics	1.3
<i>Total preventative</i>	59.2
Antimicrobials	17.3
Feed Additives POM	4.9
Hormones (including Breeding Management)	2.1
Anti inflammatories	4.0
Others	2.4
<i>Total therapeutic</i>	30.7
Feed Additives—Dietary enhancers	4
Anaesthetics	3.3
Dietary supplements (vitamins etc.)	2.5
<i>Market total value 1996 (1,800 products)</i>	£334 million

*UK animal medicine market II
1996 comparisons*

Total UK market value	£334 million
Food animals	£190 million
	(60 per cent)
(bottled water	£347 million)
UK human medicines (NHS £5,074 million)	£6,500 million
	(x20)
Prescription products	51 per cent
Merchants and saddlers	42 per cent
Free sale	6 per cent
<i>Antibiotics</i>	
NHS GPs, England only	£192 million
UK <i>all</i> animals	£80 million
<i>inc</i> UK digestive enhancers	£12 million

TUESDAY 2 DECEMBER 1997

Present:

Lord Dixon-Smith, L.
 Gregson, L.
 Jenkin of Roding, L.
 Masham of Ilton, B.
 Perry of Walton, L.
 Platt of Writtle, B.

Rea, L.
 Soulsby of Swaffham Prior, L.
 (Chairman)
 Walton of Detchant, L.
 Winston, L.

Memorandum by Professor David J Bradley and Dr David C Warhurst**DRUG RESISTANCE IN HUMAN MALARIA**

1. *Background*
 - 1.1 Malaria in the World
 - 1.2 Malaria imported into the United Kingdom
 - 1.3 Human Malaria
 - 1.4 Antimalarial Drugs
2. *Development of Resistance to the Main Antimalarials*
 - 2.1 Diversity of Resistance Patterns
 - 2.2 The Current Situation
 - 2.3 Consequences of Resistance
3. *Responses to Resistance*
 - 3.1 Coping
 - 3.2 Prevention
 - 3.3 By-passing
4. *Needs*
 - 4.1 Globally
 - 4.2 In relation to Developing Countries
 - 4.3 In relation to the UK

1. BACKGROUND**1.1 Malaria in the World**

Malaria is the most important parasitic infection of man as a cause of illness and death. Its distribution is throughout the tropics and subtropics. Before 1950 it occurred on a massive scale, for example it was then reckoned to cause 100 million cases of disease and a million deaths annually in India alone. With the advent of DDT as a long-lasting insecticide, attempts were made between 1950 and 1970 to eradicate malaria from the world. Europe, the USA, and many islands were freed from malaria, and its incidence was greatly reduced in Asia. Little impact was made in Africa. Resurgence followed the collapse of the eradication programme, and today some 2,000 million people are exposed to the risk of infection, several hundred million become infected or get ill from it each year, and some 2 million die annually.

Natural rates of malaria transmission vary greatly in different parts of the world, depending on mosquito habits, so that people in malarious parts of Asia may be bitten by an infectious mosquito about once a year, whilst the rural Tanzanian may receive an infectious bite more than once nightly. Sub-Saharan Africa is particularly malarious, and children become infected in the first year of life. Most of the people who die of malaria are children in Africa. But malaria occurs throughout the tropics and sub-tropics.

During the period since 1970 the loss of morale among those responsible for malaria control meant that malaria steadily increased. By 1992 a new global policy had been developed, which for the first time put primary emphasis upon early diagnosis and prompt treatment (rather than upon controlling transmission), upon malaria as a disease rather than as a transmissible infection, and this policy was agreed at an interministerial conference in 1992. It had the effect of increasing reliance on antimalarial drugs at a time when drug resistance, first a concern in 1960, became increasingly important.

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[Continued

During the eradication era, there was great concern about the spread of insecticide resistance in mosquitoes. Now that the emphasis globally is on malaria control, the spread of resistance to the common and inexpensive antimalarial drugs used for treatment and prophylaxis is the leading cause for concern in the fight against malaria.

1.2 Malaria imported into the United Kingdom

Malaria is currently not transmitted within the UK, but people who have contracted the infection overseas may become ill in the UK. The level of imported malaria depends upon the amount of malaria being transmitted in the world and the amount of overseas travel by UK residents. Over the last decade there have been, on average, about 2000 cases of imported malaria in the UK annually with an average of seven deaths each year. Over half the cases have been of falciparum malaria. The proportion due to malaria breaking through prophylactic drugs has gone up.

1.3 Human Malaria

Human malaria is an intermittent fever caused by one of four closely related protozoan parasites that proliferate within the red cells of the blood. They are transmitted by the bite of female mosquitoes of the genus *Anopheles*, within which the parasites undergo development, as was shown precisely a century ago by Ronald Ross. Of the four parasites, which belong to the genus *Plasmodium*, one—called *P.falciparum*—is much more serious than the others because the parasitized red cells tend to clog up the blood capillaries of the brain, giving rise to cerebral malaria which is manifested by unconsciousness and a high risk of death. Much of the attention given to malaria is devoted to *P.falciparum* for this reason, and this parasite is also the main one which has become resistant to drugs.

Malaria parasites are inoculated into the blood by the bite of an infectious mosquito. They first penetrate into cells of the liver and develop there for several days before bursting out in large numbers to invade red cells. In *P.vivax* and *P.ovale*, two other malaria parasite species, the liver stage may be prolonged for nearly a year, or even more. This is partly an adaptation to short transmission seasons in cooler climates. The only established drug that kills the liver stages is primaquine. The parasites undergo successive developmental cycles in the red cells, each lasting three (*P.malariae*) or two days (the other species) and leading to an 8–32 fold increase in parasite numbers. The disintegration of the red cells leads to an attack of fever which therefore occurs every other day in most forms of malaria, while the parasite numbers increase logarithmically at each cycle, causing increasingly severe illness until either treatment with drugs or an immune response supervenes. Untreated, the mortality from a first falciparum infection is very high.

1.4 Antimalarial Drugs

There are less than a dozen antimalarial drugs in regular use in the world. Details of them and of mechanisms of drug resistance are given in the technical appendix. Drugs may be used to treat clinical malaria, to remove residual parasites from the liver of those who have been clinically cured, or taken on a regular basis to prevent infection, as chemoprophylactics. Quinine has been in use for centuries as a rapidly effective but relatively toxic drug, and is the standard intravenous treatment for life-threatening malaria. Since 1950 it has been superseded worldwide as the first-line antimalarial treatment for the uncomplicated disease by chloroquine which is cheap, rapidly effective and given by mouth. Widespread resistance to this drug is of the gravest concern. Proguanil and pyrimethamine interfere with the folate metabolism of the parasites (as do sulphonamides at another stage) and resistance to these drugs develop rather rapidly. More recent drugs include mefloquine, halofantrine, some of the tetracyclines, and derivatives of artemisinin. Malarone has just been licensed for treatment. Several more drugs are in a late stage of development. Each has advantages for particular situations and drawbacks. Rapid action is of importance for treatment drugs while low toxicity is specially relevant for prophylactic use. Primaquine is able to destroy persistent parasites in the liver.

2. RESISTANCE TO ANTIMALARIAL DRUGS

2.1 Diversity of Resistance Patterns

Resistance of *P.falciparum* to antimalarial drugs is characterized by two contrasting features: great diversity in the local rate of acquiring resistance to particular drugs and also an inexorable global spread of resistance to an increasing number and proportion of the available antimalarials. It is a losing battle, using ever more costly drugs, but not without rays of hope. The problems are apparent for the UK traveller faced with the increasingly difficult choice of prophylactic antimalarials, balancing efficacy against issues of cost and of adverse effects, but the deepest worries are for impoverished populations of highly endemic areas, especially in Africa, where it is increasingly difficult to treat attacks of life-threatening disease in children.

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[Continued

For some antimalarial drugs, the genes for resistance seem to be present at low levels in natural *P. falciparum* populations. Consequently use of the drug leads to rapid selection of resistant strains. Pyrimethamine, an anti-folate drug, is the clearest example. It was used on a village scale as a prophylactic several decades ago at Mtu wa Mbu ("the place of mosquitoes") in Tanzania and in less than a year the malaria parasites were resistant. Its use was terminated. Resistance has remained, and spread about 10 km each decade since then.

At the other extreme is chloroquine resistance. The drug was introduced at the end of the second world war and, because of its low cost and efficacy, was—and still is—used to treat malaria attacks throughout the world on a huge scale. Much of Africa's population probably receives one or more treatment courses of chloroquine annually. Resistance was first detected, about a decade after its introduction, in Colombia in 1960, and shortly thereafter on the Thai-Vietnam border. It has gradually spread to involve the whole Amazon basin in the New World, and extended from Thailand throughout all SE Asia, and to a much lower degree through India. From there it seems to have reached East Africa by ship around 1983. Chloroquine resistance has spread through Africa from East to West and has practically reached every country south of the Sahara. It seems clear that chloroquine resistance requires rare mutations to arise *de novo*, but that drug selection pressure allows the spread of these genes widely. Indeed, one can make a plausible case that the original chloroquine resistance genetic change has only occurred twice, and its spread has been due to diffusion of the resistant strains.

2.2 The Current Situation

At present, *falciparum* malaria strains resistant to chloroquine occur over most of its range except for central America, parts of the Middle East and Haiti. Resistance to pyrimethamine/sulphadoxine, the other low cost treatment regimen, is widespread in Africa, SE Asia and South America. Resistance to pyrimethamine is widespread throughout the world as is partial resistance to proguanil. Mefloquine resistance is substantial only in localized parts of SE Asia. Multiple drug resistance, including partial resistance to quinine, is now a major problem in south-east Asia. Resistance to the low-cost antimalarials is now of great concern throughout most of Africa south of the Sahara.

Strains of *vivax* malaria resistant to chloroquine have begun to appear in areas of SE Asia.

2.3 Consequences of Resistance

The consequences of the current degree of antimalarial resistance are massive, especially in Africa where Ministries of Health, with annual budgets of a few dollars per head, have to decide whether to abandon chloroquine as the first line treatment drug, pyrimethamine-sulphadoxine as the next, and to move to very expensive alternatives.

For travellers from the UK, the question is whether to go for more efficacious (and often more expensive) drugs for prophylaxis at the price of more frequent or more unpleasant side effects with the resulting use of health staff time and intermittent media crusades or whether public awareness can limit the consequences of break-through malaria on less efficacious drugs.

3. RESPONSES TO RESISTANCE

What can be done to deal with the problems of drug-resistant malaria? Possible actions fall into four categories: coping, preventing, by-passing and management.

3.1 Coping

Currently antimalarial resistance is a massive problem for treatment of the disease in Africa and Asia and a substantial difficulty for prevention in travellers from the UK. The problems will worsen, even if feasible preventive measures are taken. Coping requires better use of available drugs and the development of new antimalarials. Economic pressures make both more difficult.

In SE Asia where the main problem is the very high degree of resistance to almost all available drugs, the main need is for new drugs. The actual case incidence is not overwhelming, but there are difficulties in managing individual cases.

In sub-Saharan Africa, where there is now very widespread chloroquine resistance and increasing resistance to Fansidar and other drugs, there are problems at both policy and individual levels. The economic implications of changing from chloroquine as a first line drug are very great, and if Fansidar is also abandoned the drug budget soars. When low cost drugs are kept for general use, it is necessary to have good referral systems of patients to hospitals adequately supplied with second line drugs. The situation for young children, on whom most mortality falls, is especially difficult as they get ill frequently and may get into a life-threatening state rapidly.

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For UK travellers, the problem is on a much smaller scale, but is of practical concern to UK citizens. Here the difficulties are of compliance with chemoprophylaxis. Cost is much less of a problem than for impoverished villagers, but may still be appreciable relative to the cost of a holiday. Relatively healthy holiday travellers are very intolerant of side-effects. Once chloroquine resistance is prevalent in a destination area current options are between taking 16 tablets a week with a significant change of side-effects, or one weekly with an increased chance of neuropsychiatric problems (and a bad press).

All these situations point to the needs for new drugs to be available. They should be preferably of a different chemical structure from current ones (to reduce the chance of cross-resistance), of modest cost to make them attainable by developing country populations, and effective against all malaria species. For travellers, prophylactic drugs should ideally prevent establishment of the liver stages of the parasites—such “casual prophylactics” have the advantage that they could be discontinued on returning to the UK.

3.2 Prevention

Resistance becomes a problem only when a drug is used on a large scale. Where resistance is a multistep process, the presence of people with rather low concentrations of a drug will provide selective pressure for the lower levels of resistance, which could not withstand high drug levels. The low levels arise when many people are taking inadequate doses of antimalarials or when antimalarials with a very long half-life are used in a very high transmission area.

On the whole, resistance is generated in long-term inhabitants of endemic areas. Short-term visitors lack any acquired immunity and usually get ill when infected, with consequent treatment before they become a risk to others.

Adequate control of the drug supply is a key aspect of preventing the emergence of resistance, or at any rate of delaying it. Medicines are available in an uncontrolled way in many developing countries. High cost unnecessary drugs are often aggressively marketed in the private sector when they are not yet needed for case management. Consequently, resistance to them may be established by the time that they are really needed. It is difficult to develop an effective licensing policy and to enforce it. UK companies are not blameless in these matters.

3.3 By-passing

If the transmission of malaria can be reduced sufficiently by other means, the need for antimalarial drugs for treatment and prophylaxis will be greatly reduced and also selection pressure for resistance will fall. The best long-term hope for this is an effective vaccine or vaccines. Other approaches to transmission control, whether by traditional means such as environmental vector control or residual insecticide spraying, or by more innovative methods such as insecticide-treated mosquito nets or, in the future, genetic engineering of mosquitoes, can reduce the need for drugs.

4. NEEDS

The UK can helpfully act in three areas.

4.1 Globally

New drugs, development of vaccines which conceivably could make drug treatment a minor activity, and development of new methods of malaria transmission control are all needed and it is immaterial where they are initially devised. There has been a renaissance of support for malaria research and control in the last few years, especially in relation to Africa. The UK has occupied a leading rôle in malaria research for many years. Increased support for malaria research both from and by the UK is needed.

New drugs are generally developed by the pharmaceutical industry, which is not strongly motivated to produce more medicines for impoverished people. Nevertheless precedents have been set in support of antiparasitic drugs, both their development and marketing, in collaboration with WHO, to benefit less developed country populations. These should be encouraged by the climate of opinion, appropriate tax relief, and support of the collaborating international agencies.

4.2 Action in relation to malaria endemic countries

Some countries are seeking to get strict registration of pharmaceutical imports and then to enforce regulatory policies to prevent widespread marketing of drugs in the private sector when this is premature for clinical needs, contrary to the public health, and liable to speed the emergence or spread of resistance. The UK government

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needs to be supportive of such efforts and not to allow cries for “free trade” to produce policies against the public health. Appropriate pressure should be used to discourage UK firms from finding ways to violate the public health while remaining within the law.

The UK needs to support bilateral and multilateral attempts to develop a rational policy framework for countries to decide when to change their first and second line drugs for malaria treatment in national programmes and to have a list of appropriate drugs that may be sold. The UK needs to continue its support for surveillance programmes for drug resistance and to build overseas capacity to sustain the programmes and interpret their results.

In very poor countries it may be appropriate for the UK to fund the availability of more expensive second line drugs than can be locally afforded. This should be firmly linked to better regulation and licensing of drugs.

4.3 Action in relation to UK imported malaria

Prophylaxis is better than treatment and the UK needs to maintain a supply of balanced information on malaria prevention to travellers. Special attention needs to be directed to members of ethnic minority groups from Africa and South Asia who have both high malaria attack rates and very low rates of compliance with chemoprophylaxis. The current perverse weighting against prophylaxis and for vaccines needs to be corrected.

As the genetics of resistance become clear, it is necessary to fund a reference service for detection of drug resistance genes in specimens from patients. This can also be used to provide data for endemic countries. Surveillance needs to be maintained, and it is essential to obtain regular data on the prophylactics used, through the international passenger survey.

More broadly, the UK needs to maintain sufficient expertise in the management of life-threatening drug-resistance malaria to be able to cope with the clinical problems that arise.

TECHNICAL ANNEX

Antimalarial Agents: Current Antimalarials and Mechanisms of Resistance

CLASSIFICATION OF ANTIMALARIALS

Antimetabolites, usually antifolate drugs, are active against all the growing stages, including those in the mosquito. They are effective on tissue—and to some extent on blood-schizonts and on the sporogonic stages. The growing preerythrocytic stages in the liver (liver schizonts), erythrocytic stages in the blood (blood schizonts) and growing stages in the mosquito (sporogonic stages) are all affected to a greater or lesser extent. Their action on the tissue schizonts means they are “causal prophylactics” which prevent the development of the infection in the liver. The antimetabolites are divided into two main groups, each acting on different stages of the biochemical pathway from para-amino benzoic acid (PABA) to tetrahydrofolate co-factors essential in the synthesis of the pyrimidine thymidylate for DNA.

TYPE I ANTIFOLATES

Sulphonamides and sulphones, which are slow acting and weakly anti-malarial alone, mimic PABA in chemical structure. They compete with PABA for the first enzyme in the pathway of tetrahydrofolate synthesis, dihydropteroate synthase (DHPS), and react with it to give toxic dihydropteroate analogues which block the next enzyme in the pathway, dihydrofolate synthase. This part of the pathway is undeveloped in mammals which obtain dihydrofolate by reduction of dietary folate, and so it represents a unique target for these drugs in malaria parasites and other micro-organisms.

TYPE II ANTIFOLATES

These include pyrimethamine and cycloguanil (the metabolite of proguanil) and they mimic dihydrofolate in chemical structure. They therefore competitively inhibit dihydrofolate reductase (DHFR) which is responsible for production of tetrahydrofolate. The basis of their selective toxicity for malaria parasites is their high affinity for malarial DHFR, about 1,000 times their affinity for mammalian DHFR.

In combination with sulphonamides or sulphones (as sulfadoxine/pyrimethamine [SDX/PYR] or dapsone/pyrimethamine) the DHFR inhibitors are active in treatment (although relatively slow acting) and in prophylaxis. The combinations show potentiation.

Blood Schizontocides act only on the growing intraerythrocytic stages which are carrying out haemoglobin digestion. Their effect is rapid, and since the blood stages are responsible for malaria pathology these drugs are preferred for treatment. Blood schizontocides are concentrated actively from the plasma by the intraerythrocytic

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malaria parasites. These weakly basic drugs become trapped within the acidic digestive vacuoles (lysosomes). In addition to this lysosomotropism it appears that these drugs bind to released haemin to give membrane- and enzyme-toxic complexes. Normally, malaria parasites detoxify haemin residues as crystalline, non-toxic malaria pigment (haemozoin).

Chloroquine has been used widely as a prophylactic of low toxicity, although it has no effect on the liver stages and only prevents the development of the blood forms. This is termed "suppressive prophylaxis".

Blood schizontocides can be divided into type 1, chloroquine-like (amodiaquine, amopyroquine, mepacrine) and type 2, quinine-like (mefloquine, halofantrine) groups. Cross-resistance develops more or less readily among type 1 blood schizontocides, but infections which are moderately resistant are treatable using type 2 blood schizontocides.

In the early 1960s strains of *Plasmodium falciparum* from S America and S E Asia began to show signs of resistance to chloroquine, after about 10 years use of the drug for prevention and treatment. In 1978 resistance was found in East Africa and since then it has spread to Central and West Africa. Now reports of chloroquine resistance encircle the globe, from S America to Vanuatu in the Pacific.

Chloroquine resistance seriously compromised treatment and quinine, once discarded as too toxic, is now routinely used as a treatment for chloroquine resistant *falciparum* malaria. In Thailand, however, where quinine has replaced chloroquine for treatment since about 1978, there is now a significant amount of quinine—(and, in some cases mefloquine—) resistance in areas bordering Myanmar and Cambodia.

Although chloroquine resistance in *P. falciparum* is known to encircle the tropical world, chloroquine is still used as a first line drug in many areas, and it has varying effectiveness.

There have been a few reports of chloroquine-resistance in blood stage *P. vivax* from S E Asia.

8-aminoquinolines have some effects on all parasite stages but at non-toxic doses only on dormant stages in the blood (mature gametocytes) and the growing pre-erythrocytic schizonts and dormant hypnozoites in the liver. Primaquine is used for "radical cure" of *P. vivax* and *P. ovale*, and to kill mature gametocytes of *P. falciparum*. It has been used in the past as a casual prophylactic, and as a result of the shortage of suitable prophylactic agents for *P. falciparum* in areas of drug resistance, this use has recently been revived on an experimental basis. Primaquine, is relatively inactive until metabolised (oxidative demethylation) to active quinones. These can undergo reversible reduction—oxidation and interfere with redox systems.

Although some strains of *P. vivax* from S E Asia show reduced sensitivity to primaquine, there is no serious problem of resistance.

ANTIBIOTICS

Certain antibiotics affecting protein synthesis, such as tetracyclines and clindamycin have a marked but slowly developing effect on malaria infections. They probably affect synthesis of protein on the bacterial-type ribosomes of the mitochondria. They are particularly used to follow up quinine treatment of quinine—refractory strains of *P. falciparum*. An alternative for this purpose is a sulphonamide/pyrimethamine combination. The tetracycline doxycycline is finding favour as an alternative prophylactic drug where mefloquine and chloroquine/proguanil are not acceptable.

NEW ANTIMALARIALS

The most promising are blood schizontocides.

Mefloquine (Lariam) and to a lesser extent halofantrine (Halfan) are based on the quinine structure and have been shown to be effective in treatment of chloroquine resistant strains of *P. falciparum*.

There is developing resistance to mefloquine especially in the parts of Thailand where quinine-resistance is a problem. Mefloquine is now recognised as an effective and relatively non-toxic suppressive prophylactic drug. Its use should be avoided in the first trimester of pregnancy. Estimates of the incidence of severe adverse side-effects of mefloquine prophylaxis requiring hospitalisation vary from 1/12,000 to 1/250. There can be no doubt that when this drug is used for treatment there are severe side effects in 1 per cent of patients. Because of these problems, mefloquine prophylaxis is recommended only in areas where a high transmission rate is accompanied by a high prevalence of chloroquine-resistance in *P. falciparum*.

Halofantrine, which is licensed only for treatment, is effective in chloroquine-and quinine-resistance, and in most cases of mefloquine-resistance. Its absorption from the gut into the blood (bioavailability) is variable, and it tends to lengthen the Q_t interval with toxic effects especially in persons with heart defects, or after mefloquine prophylaxis. Its use is currently restricted because of these features.

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A group of antimalarials of novel structure has been developed from the Chinese medicinal plant *Artemisia annua* (Qinghao). The active principle of the plant artemisinin or qinghaosu, is a rapidly acting blood schizonticide, active against resistant strains of *P.falciparum*. Its chemical structure is notable in having a peroxide group, and it probably acts by a free of radical mechanism. A modification, artemether, shows great promise in treatment of severe malaria, showing a more rapid effect than quinine against strains refractory to that drug. Artemisinin derivatives are embryotoxic and can show irreversible neurotoxicity in experimental animals, so are not recommended for prophylaxis.

In addition to these blood schizontocides, a new antimetabolite (Atovaquone) has been developed based on the naphthoquinone lapachol from the traditional medicine Lapacho (Surinam) heartwood. The mode of action is probably via an effect on mitochondrial ubiquinone-linked respiration. Resistance develops easily and current clinical studies are being carried out using potentiating combinations with the antifolate proguanil.

MEASURING DRUG RESISTANCE:

There are three levels at which drug resistance can be measured: (i) by detecting changes in the resistance genes in the malaria parasite's nucleic acids using the polymerase chain reaction; (ii) by observing the action of drugs on parasites cultured from the blood of patients with malaria; and (iii) by treating malaria cases with a drug and observing the course of infection.

- (i) In a few cases the molecular basis of drug resistance is known. Anti-folate resistance appears to be related to single base-pair changes in the dihydrofolate reductase gene of the malaria parasite. The location of the mutation seems to be different for proguanil and for pyrimethamine. Were this the whole story, mapping the distribution of resistance would be a relatively straightforward technical matter. However, studies comparing the genetic composition of parasites and the results of treatment have given discrepant results in some areas because of the diversity of strains, even in the same person, so that it is premature to rely solely on gene frequencies in mapping resistance in the field. Resistance to chloroquine is both polygenic and not yet fully understood.
- (ii) Malaria parasites can be cultured from the blood of infected people and the effects of drugs observed by adding them to test cultures. The results give a good indication of susceptibility to the drug, but there is only an approximate correspondence with the results of treating patients.
- (iii) Patients may be treated, preferably under conditions where reinfection is unlikely, and the level of parasites assessed after standard times. This is the preferred method for surveys.

MECHANISMS OF DRUG-RESISTANCE IN PLASMODIUM FALCIPARUM:

Change in Target Enzyme.

1. Antifolates: type 1. (sulphonamides/sulphones: e.g., sulfadoxine, sulphamethoxazole, dapsone)

They mimic PABA and bind to dihydropteroate synthase (DHPS) which normally converts dihydropteridine pyrophosphate and PABA to dihydropteroate in a reaction not found in humans.

Several single nucleotide changes (mutations) in the dhps gene change amino acid residues, giving resistance by weakening drug-binding.

CODON	436	437	540	581	613
Wild type	Ala	Ala	Lys	Ala	Ala
R	Ser	Gly	Glu	Gly	Thr
R	Phe				Ser
?	Cys				

2. Antifolates: type 2. ("antifols": e.g. pyrimethamine, trimethoprim)

Dihydropteroate is then joined to glutamate to give dihydrofolate, which is then reduced by dihydrofolate reductase (DHFR) to give tetrahydrofolate (Tetrahydrofolate is essential in the synthesis of thymidine for DNA). Antifols mimic dihydrofolate and bind to DHFR, blocking its action.

Several single nucleotide changes (predominantly codon 108) in the dhfr gene weaken the binding of the enzyme to antifols and are associated with resistance to pyrimethamine. Estimated mutation frequency in this gene is one every 5 million nuclear divisions. Important mutations differ with different drugs.

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CODON	16	51	59	108	164
Wild type	Ala	Asn	Cys	Ser	Ile
R	Val	Ile	Arg	Thr	Leu
R				Asn	

For resistance to FANSIDAR® (sulfadoxine/pyrimethamine) change in at least one amino-acid residue in each of these enzymes is needed.

3. Anti-electron transport drugs: (atovaquone and acridinediones)

These inhibit mitochondrial function by mimicking Co-enzyme Q and, blocking electron transport through the cytochrome B-C1 complex.

Mutations in the cytochrome B (*Cy-B*) gene sequence are associated with resistance, in particular a change from Tyrosine at residue 125 to Cysteine or Asparagine. Other mutations may also be involved in low-level resistance, for example Methionine at residue 132 to Isoleucine, and possibly in other genes.

Membrane Changes

Restriction on drug entry can provide a resistance mechanism which does not depend on alteration of the drug target.

Usually the drug is kept at a low level in the cell by a deficient uptake system or by being pumped out by membrane-located export pumps similar to MDR (P-glycoprotein: seen in mammalian cancer cells).

4. Blood Schizontocides: Type 1: (chloroquine, amodiaquine, quinacrine)

Resistance to chloroquine and amodiaquine in W. Africa is associated with a mutation in the gene *Pfmdr1*, Asn 86 Tyr, which codes for a P-glycoprotein homologue. PGH-1. We have shown that this mutation is selected for during treatment. In other locations the association is not so marked, and there is almost certainly another gene involved.

5. Blood schizontocides: Type 2: (quinine, mefloquine, halofantrine)

Resistance to this group, (quinine is still uncertain) depends on the overproduction of the wild-type PGH-1 protein coded for by *Pfmdr1*. This requirement for a wild type protein accounts for the reciprocal mefloquine/chloroquine sensitivity often noticed.

(Sample collection under field conditions: For the purposes of PCR, samples taken on filter paper or glass fibre paper are perfectly suitable, and they can be sent by post and stored for long periods at room temperature.)

Examination of Witnesses

PROFESSOR DAVID BRADLEY and DR DAVID WARHURST, London School of Hygiene and Tropical Medicine, were called in and examined.

Chairman

477. Gentlemen, thank you for attending and submitting evidence to us on the malaria story.

(Professor Bradley) Thank you, my Lord Chairman. I am David Bradley. I have held the chair of tropical public health at the London School of Hygiene and Tropical Medicine since 1974. My main involvement is in tropical public health in a fairly broad sense in relation to developing countries. In addition, for the past seven years I have been head of a group working on applied aspects of malaria in developing countries and how to control it. I am also co-director with Dr Warhurst of the United Kingdom

Malaria Reference Laboratory under the Public Health Laboratory Service. That is concerned with keeping track of all the cases of malaria reported within the United Kingdom. I look after the epidemiological side; Dr Warhurst looks after the diagnostic side.

(Dr Warhurst) I am David Warhurst. I have been working at the London School of Hygiene since 1976. I am currently reader in medical protozoology and co-director of the Malaria Reference Laboratory. One of my main interests is the diagnostics of protozoa and the chemotherapy or drug aspect of these diseases.

478. There is a need for new drugs chemically different from existing ones, affordable and effective.

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PROFESSOR DAVID BRADLEY and DR DAVID WARHURST

[Continued]

[Chairman Contd]

What are the prospects of the development of such drugs?

(Professor Bradley) Essentially, this is an ideal at which one aims. Drugs that are both in the pipeline and may be developed are unlikely to live up to all those criteria. On the other hand, one needs a steady supply of drugs. As you rightly say in the question, drugs will not only encounter new forms of resistance but every drug that has been produced will, after it has been in use for a while, give rise to resistance. Therefore, it is a matter of trying to ensure a steady stream of drug availability over time. For example, during the Vietnam war there was a very large US military programme to test large numbers of drugs. That led to several which entered the system. I suppose that about half the new drugs that have come in over the past decade or more emerged from that programme. When a big effort is made usually one or two drugs emerge. If that effort is not made, unless one is very lucky and something developed for another purpose turns out to have anti-malarial activity the prospects are much less good.

479. Is artemisinin reaching the market at an affordable price?

(Professor Bradley) The problem is that artemisinin has reached the wrong markets to an extent. This was originally developed from a Chinese herbal remedy. It is needed in parts of South East Asia where very widespread multi-drug resistance occurs in places where there is a good deal of malaria transmission. It costs substantially more than chloroquine and other drugs. Therefore, for poor countries it is very expensive, and is likely to remain so. It is not a particularly easy drug to prepare. It has become "too" available, in the sense that there has been a tendency to try to market it in Africa where it is probably premature to do so. If one has a limited supply of drugs the last thing you want is to have resistance to them occurring needlessly. One should wait until each one is needed before it is used.

Lord Dixon-Smith

480. What you imply is that there should be controlled release of new drugs on an international scale. As far as I am aware, there is no organisation with any support or authority to do such a thing. Do you suggest that we need to establish machinery to prevent the premature release of novel drugs in order that they can be more effectively used at a later stage?

(Professor Bradley) I suppose that in an ideal public health world that would be desirable. In practice, for many years the World Health Organization, which was the driving force behind the attempts to eradicate malaria in the 1950s and 1960s, has had a great deal of authority in relation to malaria. For example, it has been very much against the premature introduction of artemisinin. It is then up to countries who decide what drugs they license to determine what they do. Quite a number of countries in the past, in particular Kenya, have been very cautious about licensing drugs in order to try to get a controlled release of them so that they do not get on

the market prematurely. The main problem is that the system of licensing is leaky and not fully enforced in a number of countries. I think that the machinery just needs encouragement. You would know better than I whether or not it was possible to do anything more draconian than that. I doubt it.

481. A secondary question is that somebody has to develop these new drugs. We are all aware that the cost of doing so is very high. Of course, once they have done it they prefer to get a return on their investment. Therefore, there is commercial pressure which you suggest should be restricted. If it is over-restricted it may prevent the discovery or development of new drugs. You are involved in a very awkward spiral?

(Professor Bradley) Yes. As far as I understand it, the large pharmaceutical firms do not believe that they can make a significant amount of money out of antimalarials in any case. The world market is not large enough for that purpose. Therefore, there has had to be considerable encouragement through the World Health Organization and a variety of other arrangements to ensure that drug companies remain interested in producing antimalarials. It is not as though one is restricting something in which, if there were a completely free market, the pharmaceutical companies would make their fortune. It is already a more complex market than that.

Baroness Platt of Writtle

482. In paragraph 4.2 you say that the United Kingdom Government need "to be supportive of such efforts and not...allow cries for 'free trade' to produce policies against the public health." Where should they be supportive of that?

(Professor Bradley) I merely put in the remark about free trade because sometimes this is advanced as an issue when there is a discussion of this kind, as has indeed been happening. The WHO itself through its tropical diseases programme has initially encouraged a good deal of research to move forward the situation. I believe that such activity ought to be further encouraged. It has attempted in various collaborations with industry, with varying degrees of success, to move forward the production of drugs which would otherwise not be particularly remunerative to companies. There was a more ambitious scheme planned to try to get a "virtual company" set up funded by the major pharmaceutical companies in the world specifically to develop antimalarials which none of them would pursue on their own. I hear indirectly that there was a meeting about it last week and it did not take off¹. Quite a number of us were sad about that since it seemed to be a very imaginative approach.

483. You talk about supporting such efforts, but you are also speaking about delays before certain drugs are sold so that they are kept for the time when other drugs meet resistance?

(Professor Bradley) There will be markets for them in certain parts of the world, for example South

¹ Professor Bradley has subsequently learned that discussions are continuing.

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PROFESSOR DAVID BRADLEY and DR DAVID WARHURST

[Continued]

[Baroness Platt of Writtle Contd]

East Asia where there are malaria parasites that are resistant to almost every drug that is around. The degree of drug resistance varies in different places. If you were in Haiti in the Caribbean, for example, you could use chloroquine to treat *falciparum* malaria completely effectively. There would be no reason to market anything more than that. In Africa for quite a number of people chloroquine will not be adequate.

Baroness Masham of Ilton

484. A year or two ago an Oxford lecturer died. As a result, quite a lot of concern has been expressed since that involved one of the new drugs?

(*Dr Warhurst*) I believe that she took chloroquine.

485. People are worried and sometimes feel ill when they take these drugs so they do not continue with it.

(*Professor Bradley*) Perhaps I may distinguish what I have just been talking about; that is, on the one hand, the treatment by drugs of several hundred million people throughout the world who get malaria and preventing the two million deaths from it which occur largely in Africa. On the other, once one begins to talk about malaria chemoprophylaxis the situation is very different. Here, we are talking in the main about travellers from rich countries so that the financial issue is of less importance to the people concerned. One is dealing with those who do not start off ill and therefore will be very fussy about anything that makes them feel less well than at present. One is trying to prevent an attack of malaria from occurring. It is very difficult to get the trade-offs right. As long as chloroquine or proguanil are completely or very substantially effective that is not a great problem, but once there is resistance to those most of the other prophylactic medicines that one is driven to use to protect oneself against malaria do have a low incidence of side effects. It is very much a question of getting the balance right. We have struggled with that for some years.

Chairman

486. It is the use of malarial drugs in endemic areas which causes resistance and not the chemoprophylaxis. Presumably, the latter does not have a great impact on the development of resistance?

(*Professor Bradley*) That is correct. If someone goes to the tropics for a short visit, even if that person gets malaria when he may not get ill until he returns to the United Kingdom. In the first week or two after having become ill he is not likely to be infectious to mosquitoes. He is also likely to be sufficiently ill, if he is not an immune, to get himself treated fairly promptly—or die very promptly—and therefore will not be a risk to the rest of the population.

Lord Perry of Walton

487. You say in paragraph 4.1 that the development of new antimalarial drugs cannot be left to the pharmaceutical industry and market forces. To whom can they be left, especially in the United

Kingdom and EU because that is where our present interest lies?

(*Professor Bradley*) They cannot be left to them unaided and without encouragement. Clearly, no one other than the pharmaceutical companies is in a position to develop drugs and get them on to the market. But those companies will need more support from research done in the public sector—universities and so on—and also the various mechanisms I mentioned earlier to encourage them to go down that path.

(*Dr Warhurst*) The big problem with pharmaceutical companies is that the antimalarial market is only about US\$100 million. They need a market of about US\$300 million to justify the development of a new drug. They are therefore not encouraged financially to develop new drugs. They need to be encouraged morally, possibly by tax breaks.

Lord Jenkin of Roding

488. Do you have any idea of the form such tax relief may take?

(*Professor Bradley*) I am not an expert on the commercial aspects of drug development. Looking at the present situation, for example with some encouragement ivermectin is made available in Africa at no cost to the users. The manufacturers of Malarone, another very expensive antimalarial drug which has just been licensed in the United Kingdom for treatment, are making available about one million doses a year for use in Africa with the advice of a committee on how that can most helpfully be done. There are ways of encouraging pharmaceutical companies. I agree that that does not solve the problem of how to produce new drugs.

489. But does that imply that the price regulation scheme agrees a price with the National Health Service for Malarone which is sufficient to encourage the companies to make a million doses available in the developing world? Is that the mechanism?

(*Professor Bradley*) I think that that question would be better directed to the chief executive of a pharmaceutical company. Certainly in the case of the larger companies, the concern to appear favourably disposed towards poor countries and people who cannot afford large sums of money plays a role. I believe that the public image of pharmaceutical companies is important and that has been encouraged and worked on to some degree by the World Health Organization and others relatively effectively, but perhaps I am naive.

Lord Dixon-Smith

490. You said a while ago that a major problem was deaths from malaria in Africa. A major problem about resistance to treatment arises in South East Asia. Is there a lesson from that, or have I missed the point?

(*Professor Bradley*) The story is quite complicated. Resistance to most of the key antimalarial drugs arises wherever drugs are used but, particularly in the case of chloroquine resistance, began in

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[Continued]

[Lord Dixon-Smith *Contd*]

Colombia and the Thai/Cambodian border. It appeared to diffuse across and reach Africa about 10 years later. Basically, resistance to drugs is steadily increasing in Africa but it is 10 years behind South East Asia. Transmission in Africa is several orders of magnitude greater than in South East Asia. Even in parts of South East Asia where there is a lot of malaria one may be bitten by an infectious mosquito perhaps two or three times a year, where if one is a Tanzanian villager and one does not take any precautions one may be bitten by an infectious mosquito two or three times a night. The whole pattern of the disease is very different.

491. Is there a reason for that?

(*Professor Bradley*) The African mosquitoes are much longer lived and fonder of feeding on people than other animals. It is all tied up with the biology of mosquitoes.

Lord Walton of Detchant

492. As an alternative to tax relief, is there a possibility of grants towards these programmes being made under the overseas aid budget through the Overseas Development Agency?

(*Professor Bradley*) The Department for International Development (as it now is) has been supporting the World Health Organization and a variety of other groups involved in this matter. One would have to consider whether direct support of a particular drug was appropriate. One would have to look at the competing claims on the amounts of money involved. As to tax relief and the holding back of drugs, there is a limited period during which these products are commercially protected. It may be that for some of those drugs one will have to look at the pros and cons of any extension of that period. That may provide some assistance.

Lord Winston

493. Does *Plasmodium* change its resistance if it is not exposed to these drugs? Does it revert to a non-resistant state?

(*Dr Warhurst*) There is evidence that if drugs are not used some of these organisms will probably get back to their pre-existing state.

494. Perhaps one can envisage the possibility of rotating drugs?

(*Dr Warhurst*) That is very much what we would like to work out.

Lord Jenkin of Roding

495. In other fields we have been told that that has only limited effect because resistance revives rather more quickly than it originally emerged. It might be a reducing spiral.

(*Dr Warhurst*) It depends on the rate of transmission.

Lord Winston

496. I just wondered whether *Plasmodium* was different from bacteria?

(*Dr Warhurst*) It is different from bacteria because it does not have resistance plasmids. One gets such

amplification of resistance plasmids in bacteria that a lot of these approaches are not viable.

Lord Rea

497. Referring to the effect of prophylaxis on the development of resistance, you referred to people who spent short periods in countries affected by malaria, but what about those who live permanently in malaria zones and are taking prophylaxis. Does that not contribute to resistance?

(*Professor Bradley*) Hypothetically, it could do so. On the whole, if one has a non-immune person who has come from a country where there is no malaria, lives in the tropics, and gets a strain that is resistant he will become sick fairly promptly and get something done about it.

498. I am talking of people who are taking prophylaxis all the time?

(*Professor Bradley*) If they are taking prophylaxis but not getting infected because of that it cannot contribute to the development of resistance, because the parasite must come in, flourish and be passed on. If there is a breakthrough the person will become ill. It is unlikely that that will make a large contribution. On the other hand, if somebody says, "Oh, yes. I get malaria every year in spite of my prophylaxis", he will be in the same position as people without prophylaxis.

Lord Walton of Detchant

499. How do you rate the effectiveness of the impregnated bed-net strategy?

(*Professor Bradley*) Certainly, impregnated bed-nets are the most dramatic things that have been developed in the past two decades as a means of malaria control. They have great advantages over the previous system of wall-spraying with insecticides. They use much smaller amounts of insecticides and are much more targeted. That has all kinds of advantages in terms of people, the environment and cost. On the basis of short-term studies, there is strong evidence that impregnated bed-nets can reduce the amount of malaria in endemic areas very substantially. On theoretical grounds, one may say that in places where there is relatively moderate to low transmission—that is, outside highly endemic areas of Africa—impregnated bed-nets on a long-term and short-term basis are highly effective. Within Africa there is technical controversy going on about the effects on immunity of using bed-nets in the long run, but the short-term trials show that not only does one get less malaria but the all-cause infant mortality is reduced by 17 per cent in one country just by the use of impregnated bed-nets. That is a striking reduction. At the moment, we feel that they have great potential. There are a lot of technical details as to how to run a sustainable programme with reimpregnation and so on. Recently we have devoted a lot of our group's research, funded by the Department for International Development, to that aspect.

500. Is there any danger that their greater use will produce increased resistance to insecticides?

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[Continued]

[Lord Walton of Detchant *Contd*]

(*Professor Bradley*) As with drugs, any insecticide that is used on a large scale will produce resistance. The alternative is not to use it all, which would be a problem. So far resistance to pyrethroids has not been a big problem, but no doubt it will become one in due course and we shall have to find new insecticides.

Baroness Platt of Writtle

501. How often does one have to reimpregnate bed-nets?

(*Professor Bradley*) The classical account is to do it about every six months and not to wash the bed-net more than once or so in between. We have taken a completely different approach in Tanzania—it has been developed by Dr Lines, one of my colleagues—which is to start from what people do. They say that in Tanzania they wash bed-nets about every month. One therefore reduces the amount of insecticide and uses it differently (rather as one uses “Comfort” in a washing machine); one puts it in the rinse when one is washing one’s bed-net each month. That reduces the outlay required at any one time. There is a whole set of behavioural and technical issues to reimpregnation, as with any other public health measure, which need to be solved.

Baroness Masham of Ilton

502. Are there any side-effects from the insecticides?

(*Professor Bradley*) If one has just impregnated a bed-net with a large amount of insecticide a small proportion of people will experience a certain amount of itching and perhaps a rash. On the whole, these problems are very small. If one uses the pattern just described in Tanzania and a baby drinks a whole sachet for one net it will not come to any harm. On the whole, practical problems from side-effects are very small.

Lord Rea

503. How easy is it to get such a programme accepted by a population that does not normally use bed-nets?

(*Professor Bradley*) The evidence is varied. On the whole, it has proved very popular. The immediate effect is that one gets not only less malaria—which is often not perceived quite so dramatically—but the bed bugs disappear and the particular mosquitoes which come in vast hordes and keep one awake at night disappear. It has a series of very desirable consumer benefits, if you like.

504. What about the cost?

(*Professor Bradley*) The cost of a net is significant; it is of the order of several dollars. That is the main area where there is a lot of discussion. The cost of the insecticide for reimpregnation of the nets is not very high. The problem is that its introduction has coincided with the time when there has been a move away from government programmes for the control of disease. No one was ever asked to pay to have his

house sprayed with DDT, and that cost a lot of money. Because a bed-net is viewed as something that can be sold, and the World Bank and other agencies are pushing towards self-help and much more cost-recovery and so on, the two issues are somewhat mixed up. Certainly, it costs a significant amount of money. There is a good deal of discussion as to how far the initial provision of bed-nets should be subsidised.

Lord Dixon-Smith

505. Can you identify a particular reason why research into malaria has had a renaissance? Do you agree with the statement in the recent report *Malaria Research: An Audit of International Activity* that the most promising research areas are parasite genetics and biology? If so, why?

(*Professor Bradley*) First, to look at the background, during the eradication era which ended in the 1970s there was active discouragement of research. The situation was bizarre. Everyone wanted to eradicate and not control malaria. No one was encouraged to do research. When it came unstuck, malaria workers in those countries which had not eradicated malaria became totally demoralised. There was greater research into other tropical diseases, for example schistosomiasis, than malaria, even though malaria was of comparable or greater importance. The Tropical Diseases Programme of the World Health Organization (“TDR”) which was very actively supported by the United Kingdom Government—particularly in terms of getting it off the ground—was very active in starting an interest in it. A lot of scientists came into the field because of TDR and subsequently got funding from their own governments. There was a ministerial meeting in 1992 at which Ministers of Health globally signified how important they felt malaria was and that it needed renewed effort. Following that, there have been various efforts and in the past year agencies have become very active. The National Institutes of Health in America together with the World Health Organization, World Bank and various bilateral agencies, including the United Kingdom Government, have held a series of meetings particularly directed towards malaria in Africa¹. Already substantial amounts of funding have been pledged and are coming in to support that. There has been a gradual renaissance. It is now also seen as a respectable area in which to work. Back in the ’seventies if one said that one worked in malaria everyone regarded it as not serious science, whereas now there is substantial interest on the part of the most able scientists. The main question is whether the effort is maintained. It is very easy to get a lot of agencies enthusiastic for a year or two. There is a great tendency towards fashion in international funding.

¹ Note from witness: The UK Government’s Department for International Development has had malaria as a priority area for several years and has acted on it, first centrally and more recently via its country ‘desks’. It is supporting drug resistance mapping in East Africa.

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[Continued]

[Lord Dixon-Smith Contd]

What is required is sustained funding for a significant period, not just the short term.

Lord Walton of Detchant

506. There was a major programme of attempted eradication many years ago involving spraying and the draining of swamps. One wondered whether the emergence of DDT resistance had been one factor which led to that being abandoned. I also want to ask about malaria vaccine. When I was on the Medical Research Council in the 1970s there was a lot of talk about it then. Not much seems to have happened.

(*Professor Bradley*) There has been a series of malaria vaccines using different approaches. One has come along about every five years and everyone has become very excited. The vaccine has gone into trials and following the results everyone has become discouraged. The most recent one to go through that cycle was the Patarroyo vaccine developed by a very able scientist in Colombia. That was very interesting. Early trials which were not very well designed indicated that that vaccine gave substantial protection, but a series of three very carefully designed trials conducted in Africa and Asia did not show a significant degree of protection. Initially, one showed 30 per cent protection but it was only just significant; the other two showed none at all. There is now another vaccine under trial. There was a problem about its production which delayed it for a year. In the experimental work on people in the US where people have been challenged experimentally that vaccine has given far better results than ever before. It is at a stage where it looks very good but we must see what the results are. What is clear is that the rate of production of new candidate vaccines and the diversity of vaccine approaches now is much greater than in the past. This reflects the increased impetus of research and the vast steps forward in molecular biology and genetics that have been made. The whole process is proceeding at a different pace from the 1970s when it was based entirely on an empirical approach.

507. My next question is related to the molecular biology explosion. There is a suggestion in the field of bacterial infection and resistance that perhaps the days of the traditional antibiotic as we know it may be numbered but that the possibility of developing through molecular biology a whole range of antibacterial peptides and other agents that may be effective is dawning. Is anything similar arising in this particular field?

(*Professor Bradley*) We are beginning to understand the mechanisms of pathogenicity—the ways in which malaria makes a person ill—and it may be that there are ways of interfering with that which have not been tackled before. That takes us back to the question of parasite genetics and biology raised by Lord Dixon-Smith, in respect of which the Wellcome Trust publication made a recommendation about the research areas at the more basic level to be pursued. If we once understand the whole of the *Plasmodium* genome, which is likely to occur in a few years given the very

great efforts in that regard, it will have spin-offs for drug and vaccine development and more innovative approaches. That report was making a comment about the basic science. My comments have been about approaches related to specific interventions. Of crucial importance is the maintenance of a balanced programme between basic biology, strategic applied work to get at particular interventions, whether they be drugs or vaccines, and highly applied work to see how those approaches can be applied in a sustainable way to populations which have very little money.

Lord Perry of Walton

508. May I ask the likely cost of the new vaccine?

(*Professor Bradley*) My Lord, you may ask but I am unable to answer. The history of vaccine development demonstrates that the cost of the first few doses would be astronomical in terms of the millions spent on the research. But if one achieves a successful vaccine, in time it is possible to bring down the cost very substantially. If there were a good vaccine with long-lasting effects, travellers would be prepared to pay substantial sums for it. On the back of that one could fund a great deal of the cost required to meet the needs of those in developing countries.

Baroness Masham of Ilton

509. For how long would the vaccine give protection?

(*Professor Bradley*) Until we have a vaccine we cannot say. For example, if one got 50 per cent protection from cholera for six months with the earlier cholera vaccines one was very lucky. On the other hand, a yellow fever vaccine will give one protection for about 10 years. First, one finds a vaccine and then one discovers its properties and can improve the duration of action.

Lord Rea

510. You said that fashions for the support of particular kinds of research waxed and waned and that malaria reached a low ebb a number of years ago. You have described a lot of new and exciting lines of research. Is there enough funding for all the people who are doing the research work?

(*Professor Bradley*) I do not believe so. Even though there is a rise at the moment it is clear that substantial areas remain not fully funded. I particularly worry about downstream research. Once one has a new drug, vaccine or mosquito net there is a great tendency to commend the scientists concerned, but there are a lot of steps between that and the people in the village not being ill any more, both operational research and implementation.

511. Do you believe that more funding should come from the Medical Research Council and the World Health Organization, in so far as the WHO can itself get funds, or do you see the charitable sector playing a part?

(*Professor Bradley*) Certainly, there is a need for funding through MRC and WHO. In the charitable

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[Continued]

[Lord Rea Contd]

sector the Wellcome Trust has played a very substantial role, but the more traditionally "charitable" charities—the voluntary agencies, for example—have taken a much greater scientific interest in making sure that their programmes work than they did. The larger British charities (e.g. Save the Children, Oxfam) have a very good record of being very professional about the interventions they support. I can speak about needs for more funds from an area that I know most about because I sit on a committee which deals with research funding from the Department for International Development. When that began in 1990 that committee could just spend the amount of money available. Now large numbers of good projects in malaria and other fields in developing countries are being turned down which would certainly deserve funding if there were adequate funds available.

Chairman

512. With respect to prophylaxis and vaccines, in paragraph 4.3 of your paper you say: "The current perverse weighting against prophylaxis and . . . vaccines needs to be corrected." Can you explain that?

(Professor Bradley) This is a specific local United Kingdom difficulty. Two years ago the Government decided that travellers should bear the cost of their prophylaxis. The implication was that they should pay for their antimalarial drugs and for vaccines when they went away. That seemed to me to be a straightforward political decision. One can argue: "Why should the taxes of the poor pay for the travel of the rich?" But when it came to implementation, for technical reasons, (which I believe were to do with the remuneration of general practitioners—I may be wrong), they felt that they could not implement the vaccine part of it. Therefore, at present one has the slightly bizarre situation in which people must pay for their antimalarial prophylaxis which has been shown to be cost-effective according to the most conservative calculations, whereas they do not have to pay for vaccines which are much less cost-effective in comparison with antimalarial chemoprophylaxis. Therefore, by accident one has a situation that is bad for the public health. It seems to me that a person should pay for all of them or none of them. I believe that that situation is now under review by government.

513. Of course, you are talking of vaccines other than malaria vaccines?

(Professor Bradley) Yes.

Baroness Platt of Writtle

514. The Medical Research Council tells us that it is supporting "basic research into the factors that predispose some individuals to succumb to severe malaria, while others develop only mild disease." Is that a promising line of attack?

(Professor Bradley) It is a very important line of attack. Historically, the epidemiology of malaria has been one of transmission of parasites, not an epidemiology of disease. Now an epidemiology of disease is developing. I do not believe that the research

will lead to a simple way of deciding who should get chemoprophylaxis. But it is important to understand why there is a variation between people. At the moment, we do not know why it is that some children become very ill and die in an endemic area and others do not.

515. Are there any clues?

(Professor Bradley) There are a lot of clues but we do not know which ones are really important. Is it that that child happened to get more parasites from the mosquito that bit it? Is it due to variations in different strains of parasite, or how virulent they are, within the species *P falciparum*, or is it due to variations in the genes of the person and his or her particular responses? There is a lot of very good research being done on this matter at the moment, particularly that supported by the Medical Research Council and the Wellcome Trust. It is an area in which the United Kingdom has done excellent work. If we understood these matters we would at least be able to be more rational in our approach to control.

Lord Winston

516. What is the relationship between haemoglobins and resistance to disease?

(Dr Warhurst) Practically all of the haemoglobin polymorphisms are related to resistance to malaria.

517. What is the mechanism?

(Dr Warhurst) People who have sickle cell haemoglobin genes from both parents die before they reach adolescence, but people who are heterozygotes and who have a normal haemoglobin gene from one parent and a sickle cell gene from the other are protected against some forms of malaria. That is a very important protection. The gene in West Africa has a penetrance of 20 per cent. It is held there by a balanced polymorphism, that is, balancing the deaths of the homozygotes and the extra-survival of the heterozygotes. The impact of the other haemoglobin variations is being studied extensively.

Lord Walton of Detchant

518. There are also certain enzymatic constitutions which are inherited and which confer resistance?

(Dr Warhurst) Yes, for example, glucose 6 phosphate dehydrogenase deficiency.

Lord Winston

519. I just wondered whether much was known about the mechanism.

(Dr Warhurst) The mechanism of the sickle cell is to do with the easy crystallization of deoxyhaemoglobin which has the sickle cell characteristics. Under low oxygen tension in the tissues the haemoglobin tends to crystallize and damage the red cell membrane, causing the red cells to be taken out by the spleen.

520. I am concerned with the relationship with malaria?

(Dr Warhurst) In malaria the malaria parasite puts the red cell under more stress and more acid conditions. The acidity leads to the release of oxygen from the

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[Continued

[Lord Winston Contd]

haemoglobin, giving deoxyhaemoglobin, so the malaria-infected red cells are more likely to be removed from the system in a person with sickle cell anaemia, but sickle cell anaemia makes their lives worse. But in a person whose sickle cell characteristic is a heterozygote it means that the malaria-infected cells are removed from their system.

Lord Jenkin of Roding

521. At the end of your paper you say that it is necessary to have a "reference service for [the] detection of drug resistance genes in specimens from patients." Do we not have such a service at the moment?

(*Professor Bradley*) The Malaria Reference Laboratory deals with identification and gets very good support from other laboratories who refer material to us so that we can confirm the standard diagnosis. At the moment, as a routine we do not genotype the specimens because that requires very substantially more work, and the results are not readily interpretable. As the utility of genotyping becomes established it will require extra support. We anticipate that the Public Health Laboratory Service will supply it. However, I know that the Service is under continuing financial pressure. I understand that next year its budget may even go down. Therefore, as with other activities it is hoped that PHLS will not be squeezed to the point where one cannot conduct that activity. Once that reference genotyping service is provided its main value will initially lie, not in the management of the particular patient today, but in formulating policy for the future.

522. As we have heard, the unravelling and identification of the genes that confer resistance is a very promising line of research. It seems to me to be very short-sighted if, having got as far as you have with your reference laboratory, you do not have this last bit added to it. Do you agree?

(*Professor Bradley*) Yes. We shall ask for it but whether we receive it depends also on other pressures on PHLS funds.

Chairman

523. You say in 1.2 of your paper that over the past decade there have been on average about 2,000 imported malaria cases annually, with seven deaths each year due mainly to *falciparum*. Shortly, the Kyoto global warming conference is to take place in Japan. If you believe in global warming, can you look ahead to a time when malaria returns to this country and it is transmitted within the United Kingdom, for example in the fens?

(*Professor Bradley*) In the last century and earlier in the fens there was indeed transmission of malaria.

Baroness Platt of Writtle

524. And on the marshes of Essex?

(*Professor Bradley*) Yes. There is still, I believe, a stockpile of insecticide in case there is an outbreak in

the marshes of Essex! We must keep an eye on it. As temperatures rise in the United Kingdom the possibility of transmission is more likely, but it must be kept in proportion. For example, Italy's temperature is 2°C higher than the United Kingdom's but, because there has been good malaria eradication and subsequent surveillance in Italy, that country does not have malaria. With reasonable resources I believe that it would be possible to prevent the re-establishment of malaria in the United Kingdom. Nevertheless, as global warming occurs it will increase the chance of local transmission. The two cases which have occurred in the past 30 years in the United Kingdom have probably resulted from a mosquito which hitchhiked on an aeroplane from West Africa. They both occurred during an extremely hot summer. To be frivolous for a moment, it is believed that the mosquito got off the plane with the pilot, travelled in his car with him, went round to a public house near Crawley and while the pilot had a drink the mosquito bit the inn-keeper who nearly died of malaria. However, the real difference as a result of global warming will occur in countries where there are hilly areas, also highly malarious plains. For example, in Ethiopia, Kenya and parts of Uganda malaria is tending to extend up the hills. Research done by an Ethiopian worker based in our laboratory has shown that malaria has moved up the mountains a substantial distance and that the more dangerous type, *falciparum*, is occurring more commonly at higher altitudes. Further, the El Niño phenomenon is highly predictive of malaria epidemics in some countries.

525. Has anything to that effect been put before those who are considering global warming?

(*Professor Bradley*) They have had a great deal on that, in some respects perhaps too much. There is a tendency once one gets down to examples in discussion of disease and global warming to fasten on to vector-borne disease, particularly malaria. What we have relied on largely are mathematical models of potential risk. These are of some help but they provide a very over-simplified picture.* There are many other factors, such as land use changes, that affect malaria. In the United Kingdom we are trying to build up empirical evidence of the effects of temperature change on transmission in different parts of the world so that the mathematical modelling exercises, which are valuable but lend themselves to over-alarmist interpretation, are backed up by analysis of what has already happened.

Lord Gregson

526. The mosquito-breeding potential of marshland in the United Kingdom is now only a tiny fraction of what it was a hundred years ago—much to the chagrin of Greenpeace. If you bring back the marshland you can breed some bugs.

(*Professor Bradley*) That is true, but may be far different from malaria transmission.

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[Continued

Memorandum by Dr Gerald C Coles

This submission is confined to drug resistance in certain parasites of man and his domesticated animals, which is my area of research. I have listed some of my relevant publications on drug resistance in this report. This is a personal submission.

SUMMARY

Drug resistance in parasites is already a practical problem in the UK with certain human parasites. Specifically there are probably benzimidazole resistant pinworms and there are insecticide resistant head lice. In the veterinary field there are problems of drug resistance with coccidia of chickens, nematodes of sheep and horses, and sheep scab. Resistance in other types of parasites has not been adequately documented but in several cases appears to be present. To pre-empt the failure of all drugs, there is an urgent need for new tests for resistance and an understanding of the epidemiology of resistant parasites and the best way of reducing their development.

1. GENERAL

Control of parasites in both man and animals, largely, but not exclusively, relies on the use of chemicals. Regular use of chemicals is highly likely to lead to the development of drug resistant parasites.

1.1 *There are four important aspects of resistance to anti-parasitic drugs:*

- (A) *Establishing sensitive tests to detect resistance. These will preferably not involve the use of animals.*
- (B) *Determining the extent of resistance and its rate of development.*
- (C) *Determining the optimal way of using the available drugs to slow the rate of development of resistance.*
- (D) *Communicating the findings effectively to the drug users: general practitioners, veterinary surgeons, farmers and the general public.*

1.2 *Research into the resistance of parasites to anti-parasitic drugs has been so neglected at the UK, EU and world levels that adequate information cannot be given on any of the points A–C for any parasite considered in this submission. In their four year research plan, 1996–2000, MAFF failed to even mention research into parasiticide resistance management although they supported research into pesticide resistance management. Yet parasites are important human pathogens and the major issue of health in many animal production systems. Over 30 per cent of the animal health market in the UK (excluding feed additives) is accounted for by sale of anti-parasitic drugs. An Australian review suggested that of the four most important diseases of sheep in Australia over 90 per cent of losses were caused by parasites.*

1.3 *An international co-ordinated research programme on preserving drug efficacy is urgently required. There is a crucial need to evaluate the extent of drug resistance and to monitor its rate of development. In addition a much greater effort needs to be made into looking for non-chemical control of parasites.*

HUMAN PARASITES (excluding protozoa)

2. HUMAN HELMINTHS

2.0.1 *There are four major groups of human helminths (worms).*

- (a) *Gastrointestinal nematodes. Over one billion people are infected with these nematodes. They are now acknowledged as important pathogens, particularly in young children where they cause retardation of growth. They have a direct life history, eggs or larvae being ingested due to faecal contamination of food and water, or in some cases infection results from direct penetration of infective larvae through the skin.*
- (b) *Filarial nematodes which are tissue or fluid dwelling and have an indirect life history involving an arthropod/insect vector. The most notorious is *Onchocerca volvulus*, the cause of river blindness.*
- (c) *Flukes. These have a molluscs intermediate host. They are infective either by ingestion or by burrowing of larvae through the skin (schistosomes).*
- (d) *Cestodes or tape worms which all have an intermediate host. Usually only the larval stage is important as a cause of disease.*

2.0.2 *For greater detail of the drugs and problems of anthelmintic resistance see the section on veterinary nematode (Section 3.).*

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[Continued

2.1 Pin worm (UK)

2.1.1 From unconfirmed reports of treatments with mebendazole failing to cure patients, it seems likely that benzimidazole resistant *Enterobius vermicularis* are present in the UK. There has been no attempt to investigate the problem as pinworms, although very common, are not viewed as a serious medical condition.

Reference: Coles, G C (1995) Chemotherapy of human nematodes: learning from the problems in sheep. *J R Soc. Med* 88, 649–651P.

2.2 Gastrointestinal nematodes (primarily tropical)

2.2.1 Because cure rates tend to be lower with hookworms than, for example, *Ascaris lumbricoides*, it is not surprising that what appears to be the first case of benzimidazole resistance in the hook worm, *Necator americanus*, has been recently reported in Mali. I am informed that there is also probably pyrantel resistance in *Ancylostoma duodenale* in Australia. There is no information on the extent of the problem of resistance as tests for resistance need developing and validating and surveys undertaken. It must be expected that hookworms not responding to any therapy will emerge quite soon in the tropics, particularly where patients are treated in the dry season. Tests for detecting resistance and surveys for the extent of the problem are required for all human nematodes.

Reference: Geerts, S, Coles, G C and Grysel, B (1997) Anthelmintic resistance in human helminths: learning from the problems with worm control in livestock. *Parasitology Today* 13, 149–151.

2.3 Filarial nematodes.

2.3.1 Ivermectin (group 3) is being used widely for the control of *O. Volvulus*, a worm that infects millions of people particularly in Africa. The infection is transmitted by the biting fly *Simulium* which breeds in running water. It is known that not all microfilariae are removed from all patients following treatment with ivermectin and in a small minority of patient microfilariae may re-appear within two months of treatment. Whether these represent the beginning of the development of resistance is not known. The World Health Organization (MACROFIL project) is very aware of the potential for resistance and has an active research project on ivermectin resistance, the main emphasis being to try to develop a test that could detect ivermectin resistance.

Report: Sturchler, D, (Chairman) Coles, G C (Rapporteur), Buttner, D W and Venkateswarlu, A (1997). Report for the WHO, "Review of MACROFIL".

2.4 Schistosomiasis

2.4.1 Schistosomiasis (formerly schistosomiasis) is a major tropical infection affecting in the order of 200 million people and causing significant morbidity and mortality. Worms live in blood vessels and eggs are excreted via the bladder or intestine. It is eggs in tissues that cause the major pathology. The infection is transmitted by fresh water snails and the infection is thus often associated with irrigation projects. *Schistosoma japonicum* occurs in parts of the far east (Philippines and China), *S. haematobium* in Africa and the Middle East, and *S. mansoni* over Africa and parts of South America.

2.4.2 There is only one modern safe broad spectrum schistosomicide, praziquantel. Where it is being used intensively in Egypt a few cases of resistance are being found. Resistance has been found to the other major drug, oxamniquine, used specifically for treating *S. mansoni*. What is important in the development of resistance is the percentage contribution that eggs from schistosomes surviving therapy make to the infection of snails. Thus resistance is unlikely to be a major issue except where intensive mass control programmes are used, or when the people contaminating a new irrigation scheme have been treated but not cured prior to moving to the area.

References: Coles, G C, Mutahi, W T, Kinoti, G K, Bruce, J I and Katz, N (1987) Tolerance of Kenyan *Schistosoma mansoni* to oxamniquine. *Trans. R Soc. trop. Med. Hyg.* 81, 782–785.

Coles, G C and Bruce, J I (1991) Drug resistance in *Schistosoma*. In Resistance of Parasites to antiparasitic drugs. Ed. Boray, J C, Martin, P J and Roush, R T MSD AGVET, Rahway, New Jersey, pp. 51–60.

3. HUMAN ECTOPARASITES IN THE UK

3.1 Head lice

3.1.1 There has been an increase in head lice in the UK on children and this is having significant sociological implications. This increase may have been due in part to the removal of nit nurses from schools, and increased head contact due to changes in the pattern of learning. It could also be due to the development of insecticide

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[Continued

resistant lice. Our survey in both Bristol and Bath has shown resistance to both over the counter products (permethrin and malathion). We found no evidence for resistance to carbaryl but this is only available by prescription and is banned from agricultural use due to its toxicity. There is an urgent need for new products. This need could probably be met by registration of the two new flea products fipronil and imidacloprid for use against head lice. But their haphazard use would only lead to further development of resistance.

Reference: Downs, A M, Stafford, K A, and Coles, G C (1997) Permethrin and malathion resistance in head lice. Manuscript in preparation.

3.2 Scabies

3.2.2 Scabies, which is a major cause of death of foxes, is becoming more common in dogs and people. There have been no confirmed cases of resistance but there have been apparent clinical failures of treatment both in people and dogs. These have not been investigated. Misuse of insecticides on pets might result in resistance in scabies on humans.

VETERINARY PARASITES

4. VETERINARY PROTOZOA IN THE UK

4.1 Coccidiosis

4.1.1 Chickens

Coccidia are very important causes of lost production in broiler chickens by damaging the gut and reducing growth rates or killing the birds. It was the introduction of chemicals to control coccidiosis that made possible the production of cheap chicken meat.

4.1.2 Resistance has been described to all available anticoccidials. By rotational use of drugs (shuttle programmes) coccidia are still being kept under control. How close we are to loss of control is not known. The optimal way of using drugs to limit the development of resistance has not been established. At present the only test available for resistance involves infecting and treating live chickens.

Reference: Coles, G C (1994) farm animal health in Europe and the threat posed by drug resistant parasites. *Helminthologia* 31, 105-109.

4.2 Sheep

4.2.1 Coccidiosis is an important problem in young lambs causing sickness and death. The disease of coccidiosis appears to be increasing. The Dairy Sheep Association has suggested that the only modern licensed drug in the UK, decoquinate, is not any longer very effective in their animals, but this has not been investigated. Sulphonamides are also used. Other drugs used for coccidiosis control in chickens may be effective in lambs, but the market size is probably too small for pharmaceutical companies to justify the high cost of registering new products. This could be overcome by having an EU equivalent of the USDA IR4 programme whereby the USDA provides funding for registration of products for minor species, sheep being a minor species in the USA.

Reference: Coles, G C (1996) Availability of medicines for sheep and goats, *Vet. Rec.* 139, 452.

5. VETERINARY HELMINTHS IN THE UK

5.0.1 Veterinary Helminths (ruminants)

Nematodes (round worms), the most important of the helminths have a direct life history, eggs being shed in the faeces of the infected animals and larvae being ingested with herbage. They cause extensive morbidity (primarily lost production) and some infections can cause substantial mortality if left untreated.

Liver fluke (flat worm) is transmitted by a mud dwelling snail and is associated with wet pastures. Due to recent dry summers, numbers of infected animals have declined substantially. Before the advent of modern drugs in wet years very large numbers of sheep died from liver fluke infection.

Tapeworms are transmitted by soil dwelling oribatid mites.

5.0.2 Available anthelmintics for nematode control

There are only three modern broad spectrum groups of drugs, group 1, the benzimidazoles and probenzimidazoles, group 2, levamisole and pyrantel/morantel and group 3, the avermectins and milbemycins. In some countries, including the UK, there are narrow spectrum products (salicylanilides and nitrophenols,

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uncouplers) that kill the most pathogenic of sheep and goat nematodes, *Haemonchus contortus*. In some countries organophosphate anthelmintics are being used for control of *H. contortus*.

Benzimidazoles act by inhibiting polymerisation of tubulin. Low level resistance is associated with a change in the amino acid at position 200 in β -tubulin and PCR tests based on this have been developed. The changes associated with high level resistance have not been determined. Levamisole causes spastic paralysis and acts by binding to acetyl choline receptors. The molecular change associated with resistance has not been determined. Ivermectin acts on chloride ion channels in GABA receptors. The mechanism of resistance is not known but is probably not associated with a change in receptor.

5.1 *Nematodes of sheep and goats* (sheep and goats share the same species)

5.1.1 Resistance is thought to develop by selection of small numbers of worms containing genes for resistance. Resistance is transmitted during reproduction of the worms. My studies in the UK indicate that benzimidazole and levamisole resistance is recessive, but ivermectin resistance is dominant. The key issue in anthelmintic resistance is thus the percentage contribution that worms surviving therapy make to the next generation.

References: Coles, G C, Bauer, C, Borgsteede, F H M, Geerts, S, Klei, T R, Taylor, M A and Waller, P J (1992) World Association for the Advancement of Veterinary Parasitology (W A A V P) methods for the detection of anthelmintic resistance in nematodes of veterinary importance. *Vet. Parasitol.* 44, 35–44.

Coles, G C (1994) Control of parasites in sheep. *In Practice.* 16, 309–318.

Coles, G C, Borgsteede, F H M and Geerts, S (1994) Recommendations for the control of anthelmintic resistant nematodes of farm animals in the EU. *Vet. Rec.* 134, 205–206.

Coles, G C, Borgsteede, F H M and Geerts, S *Editors* Anthelmintic Resistance in Nematodes of Farm Animals, *European Community, Brussels.*

Coles, G C (1997) The genetics of anthelmintic resistance in *Haemonchus contortus* and *Ostertagia circumcincta*. (manuscript in preparation).

5.1.2 *World Scene.* In the southern hemisphere resistant nematodes of sheep are becoming a serious problem. In South Africa resistance is present to all anthelmintic groups and the first sheep farms have closed due to anthelmintic resistance. Farmers failed to take warnings seriously until it was almost too late. Resistance is also serious in the subtropical area of South America, Australia and New Zealand. So far there is relatively little resistance to group 3 in Australia and New Zealand but it is developing. Resistance to all three anthelmintic groups is present in nematodes in goats in New Zealand but the goat industry is declining fast. An official report in Australia described anthelmintic resistance as the single most important health issue facing the sheep industry.

5.1.3 *The UK scene.* In two Angora goat herds in the UK *Ostertagia circumcincta*, the most important nematode of sheep, has been found to be resistant to all three anthelmintic groups. Nematodes resistant to group 1, the benzimidazoles, are common in both goats and sheep and worms resistant to levamisole are present in the national flock. Some recent work in the south-east suggests that up to 20 per cent of flocks may have the beginning of levamisole resistance. Where farmers had not realised that an anthelmintic may be ineffective, lambs have died from worms. On one farm I was informed that about 500 died (20 per cent of purchased store lambs) before the anthelmintic was changed. Most farmers are now aware of resistance so that significant deaths should not occur until all three groups fail.

Reference: Hong, C, Hunt, K R, Harris, T J, Coles, G C, Grimshaw, W T R and McMullin, P F (1992) A survey of benzimidazole resistant nematodes in three counties of Southern England. *Vet. Rec.* 131, 5–7.

Hong, C, Hunt, K R and Coles, G C (1996) Occurrence of anthelmintic resistant nematodes on sheep farms in England and goat farms in England and Wales. *Vet. Rec.* 139, 83–86.

Coles, G C and Simkins, K (1996) Resistance to levamisole. *Vet. Rec.* 139, 124.

Coles, G C, Warner, A K and Best, J R (1996) Triple resistant *Ostertagia* from Angora goats. *Vet. Rec.* 139, 299–300.

Coles, G C (1997) Management of anthelmintic resistance. *Vet. Rec.* 140, 56.

5.1.4 Large numbers of leaflets (over 150,000) on steps to delay the development of anthelmintic resistance have been distributed to UK sheep farmers, but the evidence is that most farmers are not yet taking the problem seriously. The problem is compounded by the fact that some of the recommendations have never been validated in the field due to the lack of research funds.

Reference: Coles, G C and Roush, R T (1992). Slowing the spread of anthelmintic resistant nematodes of sheep and goats in the UK. *Vet. Rec.* 130, 505–510.

Coles, G C (1997) Nematode control practices and anthelmintic resistance on British sheep farms. *Vet. Rec.* 141, 91–93.

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5.2 *Nematodes of horses*

5.2.1 Resistance is present in the most important group of equine nematodes the cyathostomes or small strongyles. Benzimidazole (group 1) resistance is widespread and common but there is no recent estimate of the percentage of properties affected. Although not documented in the scientific literature there is some resistance to group two, pyrantel in the UK. According to two unpublished reports from both the USA and UK egg counts have reappeared in shorter periods than expected after dosing with group 3. This suggests that resistance may have started to develop.

Reference: Herd, R P and Coles, G C (1995). Slowing the spread of anthelmintic resistant nematodes in horses. *Vet.Rec.* 136, 481–485.

5.3 *Nematodes of cattle*

5.3.1 Some resistance has been reported in New Zealand, particularly to ivermectin in *Cooperia oncophora*. I am conducting a survey in the UK to see if resistance is developing in bovine nematodes. The difference between sheep and cattle is that adult sheep are treated with anthelmintic but adult cattle are not usually treated. This means that there is a large reservoir of unselected worms in the adult cattle. Worms “in refugia” (i.e., worms that escape being exposed to drug) delay the development of resistance.

5.4 *Nematodes of pigs*

5.4.1 Resistant nematodes, primarily *Oesophagostomum sp.*, have been reported in Denmark and Germany. The problem has not been investigated in the UK.

5.5 *Liver fluke*

5.5.1 Liver fluke used to be a major killer of sheep. But the advent of modern fasciolicides combined with recent dry summers, which have reduced the populations of the mud snail, *Lymnaea truncatula*, has greatly reduced the incidence. Resistance to the most active product, triclabendazole, has occurred in two western valleys in the Irish Republic and sheep died despite regular treatment. Two batches of metacercariae have been sent from UK to Australia. Dr Boray found closantel resistance in both isolates. He believes that on present trends there could be no effective modern fasciolicides left within 10 years in Australia. There are no simple quick tests for resistance and the extent of the problem in the UK is not known.

6. VETERINARY ECTOPARASITES IN THE UK

6.0.1 Resistance is most likely to be a problem in permanent ectoparasites, particularly where incompletely effective products are used. The EU registration requirements for products, which does not demand 100 per cent efficacy when products are used correctly, encourages the development of resistance. The best way of controlling the development of resistance in permanent ectoparasites is to eradicate the parasites whilst effective products are available.

Reference: Coles, G C (1996). Insecticide resistance and EU policy, *Vet.Rec.* 139, 576.

6.1 *Sheep scab*

6.1.1 Sheep scab is caused by infestation with the mite *Psoroptes ovis*. It causes an acute allergic reaction resulting in skin irritation leading to wool loss and secondary infections. It can also cause epileptic type fits. If left untreated more than 30 per cent of animals may die.

6.1.2 Because sheep scab is such a serious disease, its control was regulated by legislation for over 120 years. Deregulation was undertaken against professional advice in 1992, an action which has never been adequately explained. As a result there has been a massive upsurge in the disease (up to 25X increase from 1 per cent as determined by damage to sheep pelts) leading to widespread and sometimes inappropriate use of insecticides. With much larger numbers of mites exposed to chemicals the chances of resistance developing were large. This has led to development of resistance to two of the three available groups of insecticides, the pyrethroids and organophosphates (propetamphos). There were two cases of pyrethroid resistance in 1994–95, six in 1995–96 and 20 in 1996–97. It is expected that there will be much larger numbers this winter due to movement of sheep after use of ineffective treatments. It is quite probable that resistance to the third group, the avermectins/milbemycins (group 3 anthelmintic) has already developed, or will do so shortly. Correct oral use of group 3 anthelmintics for nematode control will result in under dosing of un-diagnosed sheep scab thus applying a high selection pressure for the development of resistant mites. It is quite probable that multi-resistant

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mites will occur within three to five years. On welfare grounds this would leave only the re-introduction of the organochlorine, lindane, or slaughter of the affected flock(s). If organophosphates are banned flock slaughter may have to start within two years.

6.1.3 The government has introduced legislation requiring the treatment of infected flocks. It suffers from two major problems. Firstly sub-clinical scab cannot be diagnosed so scab will still be spread. Secondly without rapid sensitive tests for resistance farmers will not know if they are using a fully effective product.

Reference: Coles, G C (1995). Controlling sheep scab. *Vet. Rec.* 137, 547–548.

6.2 Sheep lice

6.2.1 There are no recent reports of resistant lice (*Damalinia ovis*) on sheep in the UK, but resistant/non-responsive lice are present on goats (different species of lice). Pyrethroid resistant lice are a major problem on sheep in Australia, and organophosphates are having to be used for control. Since lice have been increasing in the UK following the deregulation of sheep scab, resistance must be expected to develop, particular where pour-on preparations are used. Pour-on treatments invite the development of resistance as they are not reliably 100 per cent effective.

6.3 Biting flies

6.3.1 There are unconfirmed reports of reduced efficacy of insecticide impregnated ear tags on cattle in the UK. Insecticide resistant biting flies are well documented in the USA and Australia.

6.4 Blow flies

6.4.1 There are no reports of insecticide resistant blow flies (*Lucilia sericata*) in the UK, but they are widespread in Australia (*L. cuprina*).

6.5 Fleas on pets

6.5.1 Because of the lack of suitable tests for resistance in fleas caught on pets, the extent of the problem of resistance in the UK is unknown. It seems likely that there is some resistance to pyrethroids and organophosphates, but with the recent introduction of three novel insecticides (lufenuron, fipronil and imidacloprid), fleas can be controlled at present. Lufenuron failure has occurred in South Africa, and in the USA fleas have been found that are resistant to all flea products except fipronil and imidocloprid. These two products have not been used for sufficient time for resistance to have emerged. It will be interesting to see how long it takes for problems of control due to lack of effective products to develop in the UK.

6.7 Chicken red mites

6.7.1 Heavy infestations of the chicken red mite can kill chickens by exsanguination. Mite infestations are a problem in chicken houses, particularly with free range birds. No survey has been reported in the UK, but from conversations with the industry it would appear that there is widespread resistance to available products. Since the industry believes products do not work they have not funded research to confirm their suspicions.

7. Conclusion

7.0.1 Resistant parasites in both humans and domesticated animals are already a practical problem and pose a serious threat to the sheep industry in certain countries including the UK. The problem of resistance can only get worse.

7.0.2 There is an acute shortage of good sensitive tests to detect resistance, and a paucity of information on both the extent of the problems of resistance and the best methods to slow the rate of development of resistance.

7.0.3 Without government recognition of the importance of drug resistance in parasites, adequate funding for research and end user education, available options for parasite control will be reduced or may even disappear. The true importance of parasites may then be recognised again.

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Second Memorandum by Dr Coles

DRUG-RESISTANT PARASITES OF SHEEP: AN EMERGING PROBLEM IN BRITAIN?

1. In 1993, the most recent year for complete figures, it was estimated, in June, that there were 43,901,000 sheep and lambs in the UK; thus these form the largest sheep flock in the European Union. The total value of the sheep industry, including companies directly or indirectly dependent on sheep farming, was put at £3.5 billion per year.¹ Sheep make a major contribution to both the rural economy and the upland landscape, where there are often common grazings. Parasites are an important cause of lost production to the sheep industry, and if left untreated, would cause unacceptable welfare problems. The major parasites are coccidia (*Eimeria crandialis* and *E. ovinoidalis*), nematodes [primarily, but not exclusively, *Ostertagia* (*Teladorsagia*) *circumcincta*, *Haemonchus contortus* and *Nematodirus battus*], liver fluke (*Fasciola hepatica*), blowfly (*Lucilia serricata* and *L. caesar*) and sheep scab (*Psoroptes ovis*). Parasitic diseases of sheep in the UK and chemical options for their control are reviewed in Ref. 2.

2. *Sheep scab* Until 1992 sheep scab was a notifiable disease and had held this status since 1869 because of its extremely contagious nature and very high mortality rates in untreated flocks.³ Since the change in legislation there has been a major increase in both scab and lice (*Damalinia ovis*) (Fig. 1). The deregulation of scab was taken against the advice of both the sheep industry and the experts (Sheep Veterinary Society) and has never been explained by the Ministry of Agriculture, Fisheries and Food (MAFF). However, since there have been claims of farmer poisoning following the use of organophosphate sheep dips, the ending of compulsory dipping and deregulation of sheep scab may have been due to fear of claims against the government. This deregulation has negated all the money and effort spent controlling sheep scab this century. It is estimated that poor-quality sheep pelts are currently costing the UK leather industry a loss of £15 million per year, but probably of greater concern than the rise in numbers of infested flocks has been the development of resistant sheep scab mites. The first case of pyrethroid-resistant mites was reported in 1995 (Ref. 4). Based on tests of pyrethroid residues in the wool along with the presence of live mites after plunge dipping the number of cases is estimated to have risen to about 20 in 1996–1997 (G D Bell, pers. commun.). Initially, resistance may have resulted from the correct use of pour-on pyrethroids to control head fly, which would have given subtherapeutic treatment for unrecognised sheep scab. How far the increase represents development of new resistant isolates and how far it has been caused by movement of sheep is not known. In 1996 the first case of organophosphate (propetamphos)-resistant mites was reported from Scotland.⁵ It is only a matter of time before isolates resistant to both insecticides are described.

3. The third acaricidal group—the avermectins/milbemycins—are administered by injection. Ivermectin, the only product licensed up to 1997, has to be given as two injections seven days apart, and does not provide protection against re-infestation.⁶ There have been a number of unconfirmed reports of treatment failures, most of which are unlikely to have been investigated. It is probable that these have arisen from mis-injection of a very few animals. Nevertheless, the possibility cannot be excluded that isolates of *P. ovis* resistant to all three groups will develop. Without novel insecticides, or a return to the organochlorine lindane, which would not be popular with environmentalists, this could necessitate flock slaughter on welfare grounds, which would be very serious where extensive common grazings are involved. The Ministry of Agriculture, Fisheries and Food has recognised the seriousness of the situation and, in an about turn of policy, has introduced legislation involving compulsory treatment of infested flocks but not compulsory dipping of all flocks. However, without diagnosis of the resistance status of outbreaks, incompletely effective treatments may be used, resulting in further sub-clinical scab and dissemination of the resistant mites.

Nematodes

4. Nematodes are less of a problem in temperate regions than in the subtropics where there is summer rainfall. In the UK, the impact of nematodes on sheep production declines towards the northern regions. The most pathogenic worm, *H. contortus*, has usually been confined to the southern part of the country. Nevertheless nematodes cause considerable production losses, and if left untreated on heavily stocked pastures they can kill lambs. Compared with the situation in, for example, Australia,⁷ anthelmintic resistance has been slow to develop in the UK. The first case of benzimidazole resistance was described in 1982. By 1990, when the first random survey of sheep farms in three southern England counties took place,⁸ 61 per cent of sheep farms in West Sussex had benzimidazole-resistant nematodes. In a second survey, in 1992, figures of 43 per cent for the south-west and 15 per cent for the North-east of England were recorded.⁹ The differences in occurrence of resistance can be accounted for both by climatic differences and by the greater percentage of upland farms in the north-east. The data for the two surveys are shown in Table 1 with the species of nematodes involved displayed in the Table 2. During the 1992 survey, the first case of levamisole resistance was found in *O. circumcincta*. The second case was documented only in 1996 (Ref.10), but it is likely that low-level resistance is considerably

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more common than the two cases suggest. The first case of ivermectin resistance was found in an experimental goat farm in Scotland in 1992 (Ref. 11). In 1996, two Angora goat farms were found with triple-resistant *O. circumcincta* (i.e., resistant to benzimidazoles, levamisole and ivermectin).¹² As this type of resistance has developed in New Zealand and been imported into Eastern Europe,¹³ its separate development in the UK from over-use of anthelmintics was not surprising. Other cases of triple resistance are undoubtedly present in Angora goat herds and, where sheep are grazed with Angora goats, it is most probable that the triple-resistant nematodes have entered the national sheep flock. It would obviously be desirable to monitor all sheep grazed with Angora goats. If further surveys were undertaken, it is highly probable that the spectrum of nematode species known to be involved in drug resistance would increase.

Resistance management

5. No programmes like the widely adopted control schemes of Australia,⁷ exist in the UK. Recommendations for control of resistance have been made,¹⁴ but some lack experimental validation, particularly regarding the merit of annual alternation of anthelmintic classes, which has been questioned on the basis of computer modelling.¹⁵ Leaflets on anthelmintic resistance have been widely distributed, but a recent survey¹⁶ suggests that many farmers are not acting on the advice and very few (<10 per cent) have had their farms tested for the presence of anthelmintic-resistant nematodes. Farming organisations have shown little practical interest in anthelmintic resistance and MAFF also appears disinterested. In MAFF's four year research plan,¹⁷ money is to be spent on pesticide-resistance management but not on parasiticide resistance management. This apparent inconsistency requires addressing by the government.

6. Resistance management of ectoparasites is also required. Research to develop new and sensitive tests for insecticide resistance and examine further the factors selecting for resistance is fundamentally important. The best way of controlling resistance in permanent ectoparasites is to eradicate while effective drugs remain. This might be possible if compulsory flock health certificates had to accompany sale of sheep. Without research on parasiticide-resistance management it is unlikely that anthelmintics and insecticides will retain their efficacy in the UK against major parasitic diseases. Therefore, unless new chemical types are introduced, or highly effective alternative therapies developed, parasites are likely to cause very considerable financial problems and serious issues of welfare in the future for the UK sheep industry.

REFERENCES

1. Sheep UK (1995) *National Sheep Association*, Malvern
2. Coles, G C (1994) *In Practice* 16, 309–318
3. Kirkwood, A C (1986) *Parasitol. Today* 2, 302–307
4. Synge, B A *et al.* (1995) *Vet. Rec.* 137, 51
5. Clark, A M *et al.* (1996) *Vet. Rec.* 139, 451
6. Bates, P G (1993) *Vet. Rec.* 19, 467–469
7. Waller, P J *et al.* (1995) *Vet. Rec.* 136, 411–413
8. Hong, C *et al.* (1992) *Vet. Rec.* 131, 5–7
9. Hong, C *et al.* (1996) *Vet. Rec.* 139, 83–86
10. Coles, G C and Simkin, K (1996) *Vet. Rec.* 139, 124
11. Jackson, F *et al.* (1992) *Res. Vet. Sci.* 53, 371–374
12. Coles, G C *et al.* (1996) *Vet. Rec.* 139, 299–300
13. Varady, M *et al.* (1994) *Int. J Parasitol.* 24, 335–340
14. Coles, G C and Roush, R T (1992) *Vet. Rec.* 130, 505–510
15. Barnes, E H *et al.* (1995) *Parasitol. Today* 11, 56–63
16. Coles, G C (1997) *Vet. Rec.* 141, 91–93
17. Ministry of Agriculture Fisheries and Food (1996). Research Strategy 1996–2000.

TABLE 1

Occurrence of benzimidazole-resistant nematodes on English sheep farms: the result of two random surveys

Year of survey	County	Numbers of farms tested	Farms with benzimidazole resistant nematodes (per cent)
1990	East Sussex	49	35
1990	West Sussex	57	61
1990	Oxfordshire	52	44
1992	Devon and Cornwall	84	44
1992	Northumberland and Durham	54	15
1992	Non-dairy goats, England and Wales	63	65

Source: Refs. 8 and 9.

TABLE 2

Distribution of benzimidazole resistance among nematode species for affected sheep flocks and goat herds in 1992 survey (Table 1)

Species	45 Sheep flocks Per cent	41 Goat herds Per cent
Ostertagia circumcincta	69	33
Haemonchus contortus	27	48
Trichostrongylus sp.	2	19
Cooperia curticei	2	0

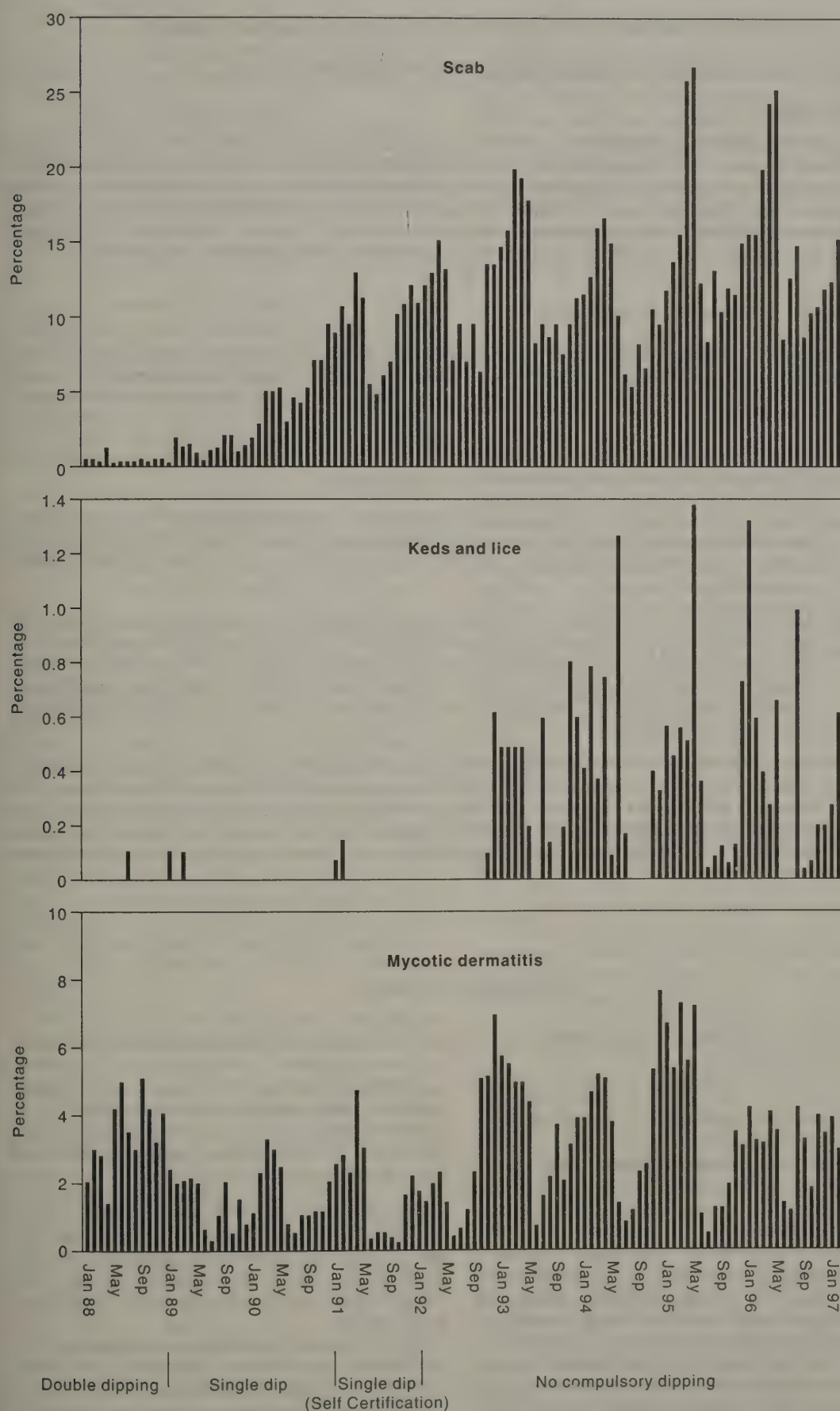
Figure 1. Percentage of UK leather production skins affected by ectoparasites 1988–1997. Data courtesy of the British Leather Confederation. Mycotic dermatitis is not a parasitic infection but gives base line data on sheep skin damage.

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Further submission by Dr Gerald Coles on resistance in parasitic helminths**1. MAFF spending on research on antiparasitic resistance management**

Example—sheep.

A progressive company spends about 2 per cent of gross annual turnover on research. If the annual farm gate value of lamb is about £1.5 billion, the sheep industry should be spending between £15 and 30 million on research and education annually. The majority of this will be on disease control as diseases are the major cause of both lost production and problems with welfare. Any sum mentioned by MAFF should be set in this context. Over what time period was the £2+ million spent? How much was actually spent on anthelmintic and insecticide resistance management rather than the longer term needs to develop alternative methods of control?

2. Ivermectin resistance in ovine nematodes

I believe that the development of ivermectin resistance in nematodes of sheep poses such a threat to sheep welfare and to the UK sheep industry that legislation is required to stop its spread via movement of animals. Where ivermectin resistant nematodes are confirmed on a sheep farm, sheep should only be allowed to be sold to the abattoir.

3. Funding for research on anthelmintic resistance in tropical helminths

- (a) The UK funds research on onchocerciasis by supporting the OCP programme. I do not know the annual UK donation. WHO-TDR spends \$2 million annually on MACROFIL, the programme trying to discover and develop new drugs to kill adult filariae and to develop tests for possible ivermectin resistance in onchocerciasis.
- (b) The WHO only supports research on vaccines for schistosomiasis. Since there is good evidence for praziquantel resistance in up to 1 per cent of patients in Egypt, research is urgently needed on praziquantel resistance. The UK should argue for a change in policy so that the WHO supports research on vaccine development, drug discovery and development and drug (praziquantel) resistance, not just vaccine research. Funding is required for drug discovery and research on resistance in schistosomes.
- (c) I have been unable to establish what is being planned by the WHO on research and monitoring of anthelmintic resistance in hook worms. There is an urgent need for funding for further research as there is a real risk that there will soon be no effective safe treatments for hook worms (*Necator americanus*). For example the only laboratory cultures of hook worms in the UK are in risk of being lost for lack of funding for their maintenance. These cultures are essential for development of tests for resistance.

Examination of Witness

DR GERALD COLES, Division of Animal Health and Husbandry, University of Bristol, was called in and examined.

Chairman

527. Dr Coles, perhaps you would begin by introducing yourself.

(Dr Coles) My name is Gerald Coles, senior research fellow at the Veterinary School at Langford near Bristol. My main research interest is drug resistance in **parasites** (not protozoa): helminths, worms and, more recently, arthropods. Before I moved to Bristol I was head of the department of parasitology at the Central Veterinary Laboratory. When that was closed down as a formal department I needed to find somewhere else to work. I have worked in the past in North America and in industry, so I have had a fairly broad traverse of drugs and parasites over the years. I believe that I set out in my submissions the major points that I wanted to bring out. Rather

than repeat them, I shall be happy to try to answer questions. However, as I say at the beginning, I do not know the answers to all of the questions that I have posed on any veterinary parasite or the human parasites that I mention.

528. Perhaps I may begin with the mechanisms of the development of resistance in parasites. Are they similar to those of bacteria (mutation, selective pressure and genetic transfer), or are there key differences between resistance phenomena in bacteria and parasites?

(Dr Coles) The key difference is that one will not get transmission of resistance from species to species. There is a mutational change in a very small percentage of the parasites and they are selected by use of drugs. As I understand from all of the

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DR GERALD COLES

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mechanisms of resistance, there is absolutely no possibility that it can transfer between species.

529. Between species of parasite?

(Dr Coles) Yes, related parasites or anything else.

530. So, there is no danger of a veterinary parasite transmitting resistance to human parasites either at the free living level or where the two occur in the same host?

(Dr Coles) As we understand things at present, none whatsoever.

531. Is veterinary drug resistance, as it were, concerned solely with livestock and domestic animals?

(Dr Coles) Except where one has parasites like liver fluke which hardly go into human beings in this country, but which is quite important in parts of Central and South America. If resistance develops to liver fluke in the veterinary field, when people are treated there may be problems.

532. So there is no threat to human health from parasite resistance other than indirectly?

(Dr Coles) Indirectly or through zoonotic parasites, but that is all.

533. Are there any zoonotic parasites that are resistant?

(Dr Coles) Liver fluke is resistant but we know very little about it. There have been two outbreaks in the west of Ireland where the best drug, triclabendazole, failed to work entirely. But I think that that might have disappeared in the drought and by the use of another drug. We know from work done by Professor Boray, who was sent two infected samples from the United Kingdom, which he tested in Australia, that they were both resistant to one drug, closantel. That is all the information that we have in the British Isles. All I can say is that at the meeting which you, my Lord Chairman, and I attended in South Africa Professor Boray said quite explicitly that he thought that in 10 years there would be no effective drug left for the control of fascioliasis in Australia. I have no idea whether that will apply in the United Kingdom.

534. You say that the whole of the sheep industry in Australia may be decimated by drug resistance to nematodes. Is it a problem of economics, or animal welfare? How big a problem is it in this country?

(Dr Coles) It is not a problem as long as there is one effective drug left. I gave an example where a local veterinary surgeon said to me that benzimidazole resistance was not that important but he had one case in which a farmer reported that about 500 out of the 2,500 lambs he had bought in for winter feeding had died. He checked the worms and found that they were benzimidazole resistant. He changed the drug and there were no problems. That is the worst case that I have come across. I have come across others where a limited number of lambs have died in a flock before it has been realised that there is drug resistance. As long as something works then technically there is no problem, but as soon as nothing works one will have to educate the public to see hundreds or thousands of lambs dying in the fields. We know that there is

levamisole resistance in sheep nematodes. The Central Veterinary Laboratory is looking at the first possible case of ivermectin resistance (group 3) in the field. We know that benzimidazole resistance is very common. My daughter who has just started veterinary practice has told me that most farmers know that if they have problems with worms after using a benzimidazole they should not use it again. That understanding now goes right down to the level of the farmer.

Lord Perry of Walton

535. What surveillance takes place in parasitic infections in farm animals? Is there anything comparable with the human surveillance programmes?

(Dr Coles) If a Veterinary Investigation Centre comes across a case it will record it, but that is not surveillance in the sense of people going to farms to see what is going on. With a grant from the Milk Development Council I have been looking at cattle nematodes in Somerset in the past summer and autumn. Subject to what is called a controlled trial in which we carry out an infection and treatment in the laboratory, we have identified the first ivermectin resistant nematodes probably in Western Europe but certainly in the United Kingdom. Resistance is beginning in cattle nematodes. As to sheep, the Central Veterinary Laboratory has been surveying about 100 farms last year and this year to study changes. Apart from that, there is no surveillance going on of which I am aware. I know that my colleagues at the Mordun Research Institute have asked for money for surveillance in Scotland, the last survey being in 1991, and they have not had much interest from the Scottish Office. In real terms almost nothing is going on and we do not know what is the real situation.

536. Do you think that we should push for more?

(Dr Coles) Yes. I would not know about resistant cattle nematodes if I had not got a grant to see whether it could be happening in the United Kingdom as it is already occurring in New Zealand.

537. Where should we look for the money to do it?

(Dr Coles) That is the great problem. The Ministry is putting nearly all of its research money into BSE and scrapie and there is no obvious other funding source for this work. It can be very applied work. The Ministry supports surveillance-type work but only if it is basic research rather than ask what is happening in the field.

Lord Dixon-Smith

538. Is there not a case for required recording at the level of veterinary practice as to what is being discovered? This action is becoming more and more necessary in human medicine at the level of general practice. Should we not do the same in veterinary practice? Probably the cost would not be too high. I do not say that it can be absorbed in general costs, but it would be part of general costs where everybody

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Dr GERALD COLES

[Continued]

[Lord Dixon-Smith *Contd*]

contributed and the actual burden would not be too high?

(*Dr Coles*) That is an excellent idea, and I would give it my support. We would then get a feel for what was going on. People say to me that it is not a problem. My reply is that I do not have any data and I cannot say that. When the Central Veterinary Laboratory undertook the first survey in southern England people laughed. They asked me why I had done the survey. I replied that it had been paid for by industry so they should not worry; it was not taxpayers' money. But one may find a problem if it is not being reported. When that survey was carried out it was found that over 60 per cent of sheep farms in West Sussex already had benzimidazole-resistant nematodes. That is not the same as saying that there is necessarily a clinical problem if farmers use benzimidazoles, but there is good evidence of resistance. We do not know what is going on, how serious resistance is and how fast it is developing. To do that research, record it and centrally collect the data would give us quite a good indication of the problems.

Baroness Masham of Ilton

539. What advice would you give vets and farmers on the use of ivermectin?

(*Dr Coles*) It depends very much on each individual farm and how much clean grazing they have; in other words, the extent to which you can take sheep away from heavily contaminated fields. It depends on whether one is taking young lambs to market in June. It is hoped that there will not be many worm problems up to June, although the general rule that worms are a midsummer/autumn problem does not seem to apply any longer in the south west. It depends very much on the management system, and the advice must be given farm by farm. As a general rule, the more one uses the drug the more likely one is to get resistance.

540. So, you should change it around?

(*Dr Coles*) We recommend that one should change the pharmacological group on an annual basis. But if you ask me whether I can provide evidence that it will be beneficial the answer is no because the research has never been undertaken.

Lord Walton of Detchant

541. In your very helpful paper you call for more research into resistance testing, epidemiology and resistance management. We have had a paper from MAFF which says that it has funded 10 research projects relating to parasiticides to the value of about £2.5 million. Are there any other bodies like BBSRC, the farming industry, the pharmaceutical industry, the European Union, the Food and Agriculture Organization which would be likely to fund the kind of research that you have called for?

(*Dr Coles*) The FAO has funded some work in South America which has been published. It gave a very depressing picture of what was going on in the sheep industry. I had a EU grant but was unsuccessful

in getting it renewed. We were told quite firmly over the phone that basically worms were not on the high priority list and unless the study was absolutely outstanding we would not get funding. I tried with others to get research started in South Africa. We were told that the study was highly relevant. We understood privately that we had asked for too much money. When we applied the second year we were told not to bother because worms were not on the priority list. In August I went on to a farm in South Africa and found that there was one effective drug in one group which was left. After that the sheep farm will have to close down. Dr Jan Van Wyk has said that the sheep industry is on the edge of almost unavoidable collapse. Those were his words in South Africa. The pharmaceutical industry does not sponsor research into resistance. Why would they want to have bad news about their products? There is a very highly competitive market place where most of the drugs are no longer subject to patent and are sold on price by smaller companies. No funding comes from that direction. I have a small grant from the Milk Development Council which is concerned with looking for resistant nematodes in cattle. There is a possibility of some more money. Whether or not I shall be successful in renewing it I do not know. I was advised that the BBSRC who apparently thought quite highly of my ideas, stated that because it was such applied work I should come back with 50 per cent of funding from industry. So far I have been unable to come up with that 50 per cent. As to MAFF, unless I look at the actual figures and see what it is spending the money on I cannot comment on funding. All I know is that if you look at helminthology at the Central Veterinary Laboratory at its peak there were 23 scientists or researchers. There are now two left. It is hanging on just by the skin of its teeth.

542. Perhaps I may be forgiven for asking a question that is quite unrelated to parasites. Bearing in mind the importance of potential transmission of infection from animals to humans, is there any evidence of reservoirs in farm animals, for example, of leptospiral infection or tick-borne infections that give rise to Lyme disease? Do they occur in the farm animal population?

(*Dr Coles*) It is outside my area of expertise. I hope you do not mind if I do not answer your question.

Baroness Masham of Ilton

543. In this area are homeopathic medicines of any use? These medicines are being sold.

(*Dr Coles*) Recently, I attended a Dairy Sheep Association meeting. I gave a talk. Following that, somebody spoke on homeopathy. I have the text in my case, and I intend to read it this afternoon on the train. I said, "What can you do for parasites?" He said, "Nothing. We do not recommend any treatment for parasites."

544. We are at the moment trying it out on ponies. One wonders whether it is a total waste of money.

(*Dr Coles*) I would say that it is.

545. What practical strategies do you recommend to control or eliminate resistant sheep scab mites,

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DR GERALD COLES

[Continued

[Baroness Masham of Ilton *Contd*]

nematodes, coccidia and the other parasites that you mention? In United Kingdom terms which are the most urgent problems?

(*Dr Coles*) I believe that sheep scab is the most dangerous one. Within three to five years we could run out of licensed products that are effective, in which case the flock would have to be slaughtered. If that flock was on Snowdonia, one might have to slaughter all of the sheep in one grazing area. That worries me much more than nematodes. As to nematodes, I think that we could run out of controls on the first sheep farms in two to three years. I hope that I am proved wrong in both cases. My two to three years is based, for example, on a conversation with the Central Veterinary Laboratory last week in which it was said that on a number of farms they discovered that levamisole did not work fully. We know benzimidazoles do not work. We know that ivermectin resistance is also being looked at. In two Angora goat herds I looked at I found worms that did not respond to anything. Therefore, where Angoras are kept with sheep and the nematodes jump across species and the sheep are sold on it will be only a matter of time with selection pressure before we finish up with worms that do not respond to anything. To me, they are the two most important examples. What are the practical strategies? I believe very strongly that in the case of all farm animals, not just sheep, when animals are sold the purchaser ought to know their disease status. I do not refer simply to parasites but viruses and bacteria. Therefore, the purchaser will know what diseases he brings on to his farm. I believe that that could transform our approach to the control of animal diseases. It can be looked at in two ways. One could have a voluntary system which involved the potential purchaser saying, "Please fill in the enclosed government-approved form. I am buying your animals and I want to know what diseases they have." The other way of doing it is to say, "If you are to sell your animals you must produce a list of the disease status on your farm." Which is better is a matter of opinion. A lot of people do not like the idea of a compulsory system. If people were educated the voluntary system might work quite well. There have been compulsory systems in New South Wales in respect of footrot. That has been extremely successful. An individual is told that if he makes a false statement on the form he can be sued in court. The Ministry will then also jump on him. If he does not co-operate he will be taken out of the sheep business. In that way New South Wales has almost completely eradicated footrot. I am following a model. It is not an original idea.

546. Is there any resistance to footrot?

(*Dr Coles*) Not that I am aware of, but it is outside my area of expertise.

Chairman] As a matter of fact, there is.

Lord Perry of Walton

547. Is the picture that you see in this country typical of that which you see in other European countries and elsewhere in the world?

(*Dr Coles*) The sheep industry is not as large in any other country in the EU except for Spain. In Spain

sheep are kept in very dispersed and arid conditions, so worms are not a particular problem. I do not know about the status of scab in Spain. The Netherlands has a small sheep population and there is a hardly a sheep farm where the first group of drugs—the benzimidazoles—will work. I believe that the picture is similar elsewhere.

Baroness Platt of Writtle

548. In your paper you say: "No programmes like the widely-adopted control schemes of Australia exist in the United Kingdom." Is there a range of such schemes in Australia, or is the only one in New South Wales?

(*Dr Coles*) This is based on an article which appeared in the *Veterinary Record*, a copy of which I can leave with the Sub-Committee. Each state in Australia produces its own scheme. The climate changes between states or between regions in states, depending on whether it is high land or low land. They have brought in these schemes which appear to have reduced the amount of nematode transmission. For example, the Wormkill programme in New South Wales had a 90 per cent uptake within two years of its launch. We have no equivalent in this country. I shall also leave behind some leaflets which companies circulate to farmers. I do not know whether they have had very much impact.

549. Do you think that the ones in operation in Australia would be practicable in this country?

(*Dr Coles*) No. The biology, relative importance of the species and farming are sufficiently different. One must try to work out a strategy for almost each individual farm. I am rather hesitant about saying that this or that should be done, the simple reason being that when seeking to manage nematodes in sheep one tries to put the sheep on to clean pasture, that is, land that has not recently had sheep on it. But when moving them on to clean pasture one is always treating with a drug. Therefore, the only nematodes that contaminate the clean pasture are those that have gone with the sheep onto that new pasture. When there was no evidence of resistance there was not a great worry. But now there is probably a low level of levamisole resistance. With dose-and-move with levamisole, one might go from the absence of any practical problem with levamisole on the farm to a clinical problem in one season. I am scared about using epidemiological principles with drugs given that it is now known that there are resistance genes floating around in the population of nematodes. Until that is investigated I would hate to give a definitive answer. However, if you had asked me that question five or six years ago I would have given a different answer.

550. Would you stick to your earlier suggestion of either voluntary or compulsory control from the point of view of reporting disease in flocks?

(*Dr Coles*) I would not use it for control. If I already had footrot on my farm I would not be worried if I bought sheep with footrot. If I did not have footrot on my farm I would want to know that any sheep I bought came from a footrot-free farm. If I have no

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DR GERALD COLES

[Continued]

[Baroness Platt of Writtle Contd]

ivermectin-resistant nematodes on my farm I do not want to buy sheep from a flock that has ivermectin-resistant nematodes. If I have no sheep scab I do not want to buy sheep from a farm that has treated sheep for that condition in the past 12 months because those sheep may have sub-clinical sheep scab which, when it moves to my farm, flares up and causes me no end of problems. The idea is that you know the health status of the animals that you are bringing on to your farm, and you can take that into account in your own particular farm situation.

Chairman

551. Let us consider for a moment the movement of animals between farms and between countries. We make quarantine regulations for all kinds of infectious diseases caused by viruses and bacteria, but when we move animals between countries we do not take any notice of what they may be carrying in their digestive tracks in terms of nematodes, resistant or otherwise.

(Dr Coles) That is absolutely true.

552. Do you have any evidence of significant resistance being carried from Australia to other countries, leading to severe effects in the recipient country?

(Dr Coles) I am not aware of severe effects in recipient countries. However, I am aware that when the Slovak Republic imported goats from New Zealand they also imported worms which were resistant to all three groups. That work was published. But very little work has been done on the movement of resistant nematodes, in part because there are not the very sensitive tests required to look at low-level resistance.

553. I have in mind the example of Malaysia which imported sheep from Australia to graze under rubber trees. Those sheep had resistant *Haemonchus* in a very short time. It was traced to Australian resistant *Haemonchus* brought in with those sheep.

(Dr Coles) I was not sure whether that particular case arose because the sheep brought it in or whether it was due to the enormous number of treatments used annually in Malaysia because the climate is perfect for *Haemonchus*.

Baroness Masham of Ilton

554. What research is being done on tests?

(Dr Coles) It depends on the particular areas of resistance that you are talking about. With nematodes, the only sizeable funding of which I am aware—I am the recipient of a very small percentage of it—comes from the World Health Organization which is very concerned about ivermectin resistance in *Onchocerca volvulus* (river blindness). That is the main drug on which WHO relies for treatment. At 8.30 tomorrow morning I shall be talking to a World Health Organization meeting in Liverpool on exactly that subject. The WHO is supportive of that work. I do not think that anyone is doing any molecular biology on resistance to levamisole. The work on

benzimidazoles has been done and just needs to be applied, but that requires a lot of money.

Lord Jenkin of Roding

555. You spoke about sheep scab, but in paragraph 6.0.1 you say, "The EU registration requirements for products which do not require 100 per cent efficiency when products are used correctly, encourage the development of resistance." That seems to be a rather serious charge?

(Dr Coles) It is. When I talked to the National Sheep Association in September that body said that it was very concerned about it. As I understand it, the requirement for products to kill permanent ectoparasites is that they need not be 100 per cent effective if used correctly. My argument is based on the experience with lice in Australia. They used pour-ons to control lice. The scientists said right at the outset that if pour-ons were used which spread round the sheep there was not always a completely effective dose at the bottom of the sheep and there would be resistance. Today, in some parts of Australia the pyrethroid insecticides are called aphrodisiacs because the lice seem to grow better when they have been treated with those insecticides than when they have not. That illustrates the point that if you leave a few insects to survive those that survive will have a tendency to be resistant. They will interbreed and populate and so resistance will develop much faster. I believe that the legislation should be changed.

556. Is there any possibility of that?

(Dr Coles) I do not know anything about the politics of it.

Lord Winston

557. I am concerned with the behaviour of farmers and vets. Who applies pressure to try to solve these problems? Is it the farmers' organisations, veterinary bodies or government?

(Dr Coles) I believe it is generally accepted that sheep farmers are very traditional people. "If father did it, I do it." It is exceedingly difficult to get them to change what they do, perhaps for financial reasons. To illustrate it, I understand that 20,000 examples of this leaflet were sent out and that an equal number were sent out by another company. On the back I offer tests for resistance in sheep nematodes. I can count on one hand the number of tests that I have been asked to run this year by sheep farmers or their veterinary surgeons.

558. Is that because of the cost?

(Dr Coles) Yes, probably. I have said that I believe it is important to know what nematode resistance a farmer has so he can use the best drug effectively, but clearly that idea is not being adopted. I give that as an illustration of the difficulty in changing behaviours. Therefore, it should not be up to farmers or vets; it should be everyone who takes it seriously. Another illustration is sheep scab. I remember a MAFF representative telling me quite recently that if in South Wales sheep scab is detected the farmer will

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[Continued]

[Lord Winston *Contd*]

inject only the sheep that he sees has the disease with ivermectin, and to save money it is done only once. That is completely contrary to the manufacturer's instructions. People then wonder why sheep scab remains a problem.

559. To what extent do these diseases affect the value of the carcass?

(*Dr Coles*) Nematodes would affect the value of the animal. If one has nematode infection the lambs take longer to get to weight for selling. Therefore, one has to feed them for longer and so loses money. Sheep scab probably does not affect the value of the carcass very much. However, the leather industry estimates that it loses at least £15 million a year due to bad pelts. More than one sheep tannery has closed down because it can no longer obtain quality pelts. It is extremely desperate about the low quality of both sheep pelts and cattle hides because of ectoparasites. The cost of damage to cattle hides is put at about £35 million a year. The total estimated damage—it is not due solely to ectoparasites but that is the primary cause—is in the region of £50 million a year in this country. To get top quality leather, which is the only thing that the industry can work with, it must import hides from Germany and Sweden which run hide improvement schemes.

Lord Rea

560. What do they involve?

(*Dr Coles*) As I understand the system in Sweden, the farmer agrees to remove all the barbed wire from his fences and will use electric fences so that the hides will not be scratched, that he will treat for lice and vaccinate against ring worm.

Baroness Masham of Ilton

561. What about warbles which come up in the hide?

(*Dr Coles*) That is effectively eradicated. MAFF has put a lot of effort into it. It made a major mistake when it allowed the free movement of animals and warble fly was reintroduced. I hope that it is now exterminated.

Lord Winston

562. Do your answers imply that government should take a stronger lead? If there is commercial pressure that is probably what is needed.

(*Dr Coles*) One needs someone who nationally owns the problem. How much time and money is put into it is not quite so important. As long as someone owns it and is trying to do something about it that is what counts. For an individual to try to do something at the vet schools is a very hard and unrewarding process.

Lord Dixon-Smith

563. Are there prospects of new treatments in this particular field, either chemical or non-chemical? In your paragraph 4.2.1 you call for an "orphan drug"

programme. Can you explain the reasoning behind that?

(*Dr Coles*) The two are not the same. When I lived in America I did a registration under what might be called the orphan drug programme. There it was recognised that if one had an existing drug, for example for the control of nematodes in cattle, it would not pay a company to register it for sheep. The work involved would not pay for the rewards that would be obtained. A scientist could go to the IR4 programme under the US Department of Agriculture and say, "We need this drug for sheep. Will you pay for it?" The department will rank it against all the other requests for registration, perhaps for antibacterials for crayfish or worm treatments for some other animal. If it agrees you can go ahead under very careful conditions. You do the necessary work and the department says that the drug is now approved for use in sheep in the United States. I suggest that if there were a similar programme in the EU—I am not suggesting that there should be a British programme—a certain amount of money could be set aside and priorities set. People could say that one needed money for horses, goats and so forth—surprisingly, almost nothing is registered for use in goats—so that scientists did the research legally and properly. Otherwise, it would be done *ad hoc* without registration, approval and so forth. You asked me about new drugs. The number of companies doing research in the area of animal health has been contracting. There have been takeovers and amalgamations. I believe that the estimated cost for producing one new drug—it is even tougher for food animals because of all the residues work required—is over US\$200 million. One then looks at the size of the market and the share required to get back that cost. I almost wonder why anyone does it. It hardly makes sense. I know that there are companies which have active leads, but there is an enormous difference between an active lead and a safe drug on the market. The general view is that it should not be assumed that there will be any new drugs coming on to the market. The exception to that has been two new flea insecticides that are selling very well in this country. They may have other applications, for example ectoparasites on cattle or sheep. One company has said that it will not bother to produce a new insecticide for sheep because the residue problem and the problem of insecticides getting into the water and environment is so great that it is not economic to do it. I go back to my earlier comment about the need for an orphan drug programme. I know that there are good insecticides used for fleas. They may be very valuable for sheep scab, but the company may decide that it is not worth marketing it.

564. In any event, presumably the current perception is that food is in over-production and so there is very little reason to worry about the problem.

(*Dr Coles*) In the short term that is a legitimate answer. However, in the longer term if you know that you will lose the activity of your drugs in more and more conditions a situation will be reached where you need something. You need to take a strategic

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[Continued]

[Lord Dixon-Smith *Contd*]

long-term view. To go back to a comment made by David Bradley, one may get funding in the short term but the problem is one of maintaining that effort. Perhaps I may illustrate it by the number of people engaged in helminthology in farm animals. Glasgow has partly closed down. The Mordun is doing something. Edinburgh is doing nothing. There is very little being done at Cambridge. Professor Jacobs at the Royal Veterinary College told me that he had given up on farm animals and he was working only on dogs and horses. He could not get any money on farm animals. There is very little being done at Liverpool. I am trying to do a little at Bristol, but I have been working on horses, dogs and fleas because I can get money for that but not for farm animal research.

565. The mind boggles that one can get money for pets but not for an economic business, except that horses include race horses.

(Dr Coles) I agree.

Lord Walton of Detchant

566. Is there a possibility that some drugs which are introduced for the treatment of human disease, of which levamisole is one, may prove to be effective in the treatment of certain animal conditions?

(Dr Coles) If one is talking about antibacterials and physiological conditions, I fully agree. However, the history of levamisole is that it was developed for veterinary use and then went into humans. The same applies to ivermectin, the benzimidazoles, the flea products and insecticides. In the parasitic world it is the sale of products to farmers which drives the research. There is then a spin-off to parasites in humans. The view is that the poor people who have parasites cannot afford the drugs, so it does not pay to do any research, as for example with malaria.

567. The health department should be made aware that this is an anxiety. Some of these drugs will have an obvious application in the treatment of human diseases?

(Dr Coles) Yes, I agree with that statement.

Chairman

568. You said that very few antiparasitic drugs were registered for goats. What about the other minor species now in this country like llamas, ostriches and deer? For example, are antiparasitic drugs licensed for lice in deer?

(Dr Coles) I have not looked into it, but I do not think so. It would not pay a company to do the residue work.

569. Either you use the drug illegally for the control of parasites in deer or you do not use it all?

(Dr Coles) The veterinary surgeon will prescribe it off licence and one can then use it. The standard view is that if one does not sell within 28 or 60 days one will not have a residue problem. Usually, if one has residues it means that one is managing very badly.

It does not pay to treat and then sell the animals. In my view, residues are not usually a problem.

Lord Rea

570. What about problems of the elimination of pinworm, head lice and occasionally round worm?

(Dr Coles) No one has undertaken the necessary simple trial of the type that would be done on sheep. You treat people and you check a few days later to see whether eggs are still being laid by worms. That excludes re-infection. We shall start that in January. A medical colleague said, "This is a nice idea. Let's do it. I will arrange it all and you count the eggs." As to pinworm it can be controlled by the introduction of pyrantel which Pfizer produces as a medical drug. It is widely sold round the world but it is not registered for use in this country. If there is resistance we can introduce pyrantel. That should be successful for quite some time before resistance develops. After that I do not know what to do. As to head lice, on the train on the way here I was correcting the final draft of a manuscript. We have shown that in Bristol and Bath there is no doubt that over-the-counter products do not work. This was a properly conducted trial in which the doctor applied the product to the children. I am very confident of that data. That leaves one registered drug for head lice, carbaryl. Except for dogs, almost every other application has been stopped because of a question mark about its safety. At the moment, there is only the possibility of combing for head lice. The two new flea products would be expected to be very effective against lice. Privately, more than one person has admitted that it has been used and it cured the head lice problem immediately. However, that was not approved use. I have not been able to liaise with the people in the companies to ask whether they are interested. At Bristol Royal Infirmary there is a set up where we can undertake clinical trials quite easily. I believe that there is hope for the production of a new drug or the use of an existing drug for the control of head lice. That research is currently being undertaken with contacts at Bristol Royal Infirmary. If that is successful we may have something that works by next summer or autumn. Currently, there is no safe effective product for head lice in children in the United Kingdom.

Baroness Masham of Ilton

571. Does Carbaryl contain organophosphates? Not long ago there was a programme about it.

(Dr Coles) I saw that programme and also spoke to the company who sold the product, malathion. The instructions clearly say, "Do not go on reusing the product if you do not get a cure." One of the things that we want to get across to people is that, if they have used a head lice product and checked the head carefully three days later and you still have adult lice crawling around, the product does not work and it should not be tried again.

572. Has Carbaryl any relationship with organophosphates? Is research being done into it?

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DR GERALD COLES

[Continued]

[Baroness Masham of Ilton *Contd*]

(*Dr Coles*) We are doing a little¹. I am supervising a registrar in dermatology for his MD. His MD is in the control and incidence of head lice. Hopefully, the first data will emerge in the press in a few weeks.

573. There is an epidemic, is there not?

(*Dr Coles*) Very much so. I asked the doctor how it had gone up and he said that he could base it only on sales figures that he had obtained from companies and health authorities. Since 1991 the increase has been almost exponential.

Lord Jenkin of Roding

574. Perhaps this is a flippant question. I was always brought up to believe that the old nursery rhyme "Queen, Queen Caroline, washed her hair with turpentine", arose because that was an effective treatment for head lice. I have never investigated it.

(*Dr Coles*) It probably would be—so is a good razor!

Lord Rea

575. One always used to use benzyl benzoate which is a fairly caustic substance?

(*Dr Coles*) That has been used for scabies but I do not think that it is registered for use on the head.

Lord Perry of Walton

576. Should the United Kingdom do more for the third world? We seem to be doing too little for ourselves.

(*Dr Coles*) There is a big World Health Organization microfilariae programme (MACROFIL). It is looking for new drugs. I sat on the MACROFIL committee that reviewed the progress. Work is proceeding well, but obviously no one will say that he has enough money for research. As to schistosomiasis

there is virtually nothing being done on drug resistance. There has been a big US programme in Egypt. I heard recently that they are finding breakdowns in treatment with praziquantel at a low rate. They now have no money. I am currently unaware of anyone in the world who is funded to look at resistance in schistosomiasis, although a Chinese doctor is supposed to be coming in January or February to study that subject for his PhD funded by the World Health Organization. As to hookworms, I was in Geneva last February and spoke to the person concerned. He said he believed that the United Nations intended to put a lot of money into the control of nematodes in children because they affected growth and learning. I said that something had to be done about resistance. I wrote to him some time ago, said that I was due to appear before this Sub-Committee and asked for any information on the subject which was available. I have not had a reply. I am not sure whether anything is happening on research in hookworm resistance. We might lose the ability to control them quite rapidly.

577. Is mass therapy one of the ways forward?

(*Dr Coles*) I am very worried about that, whether it be with sheep or people. If you can put hygiene in place then by all means use mass therapy. If you continue with the same old bad hygiene the chances are that with mass therapy you will end up with resistance.

Chairman

578. To go back to resistance in this country, there is progressively more scabies in old people's homes and places like that. Is there any resistance there?

(*Dr Coles*) No one has examined it. When we finish work on head lice my registrar is due to look at scabies, but it is much more difficult to work with. His boss was interested in it and said that he had had a number of clinical failures in the treatment of scabies. Is that resistance or not? We simply do not know. I do not believe that anyone is working on scabies. It is a nasty parasite with which to work. One is always at risk of infecting oneself.

¹ Note from witness: Both carbaryl and organophosphates inhibit acetylcholine esterase.

TUESDAY 9 DECEMBER 1997

Present:

Dixon-Smith, L.
 Gregson, L.
 Jenkin of Roding, L.
 Perry of Walton, L.
 Platt of Writtle, B.

Porter of Luddenham, L.
 Soulsby of Swaffham Prior, L.
 (Chairman)
 Walton of Detchant, L.
 Winston, L.

Notes by Dr Deenan Pillay

1. ANTIVIRAL DRUGS LICENSED FOR USE IN UK

Aciclovir	herpes simplex (HSV), varicella zoster virus (VZV)
Valaciclovir	HSV, VZV
Famciclovir	HSV, VZV, HBV*
Foscarnet	HSV, VZV, cytomegalovirus (CMV)
Ganciclovir	CMV
Amantidine	influenza A
Ribavirin	RSV, HCV*
Zidovudine	HIV
Didanosine	HIV
Zalcitabine	HIV
Stavudine	HIV
Lamivudine	HIV, HBV*
Ritonavir	HIV
Saquinavir	HIV
Indinavir	HIV

* Indicates currently unlicensed usage.

Drug resistance identified for all but Ribavirin.

2. ANTIVIRAL DRUGS IN CLINICAL TRIALS—1997

Abacovir	HIV
Nelfinavir	HIV
141W94	HIV
Nevirapine	HIV
Delavirdine	HIV
Efavirenz	HIV
ABT-378	HIV
Cidofovir	HSV, CMV
Zanamivir	Influenza A and B
Adefovir	HIV, CMV
Lobucovir	HBV, CMV
Lamivudine	HBV
Famciclovir	HBV
Pleconaril	Enteroviruses
Ribavirin	HCV

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[Continued

3. ANTIVIRAL DRUG USAGE

- *Treatment of acute infection*, e.g., HSV, VZV, CMV, influenza, respiratory syncytial virus.
- *Prophylaxis*, e.g., HSV and CMV in immunocompromised, influenza.
- *Suppression of chronic infection*, e.g., HIV, hepatitis B, hepatitis C, genital HSV.

4. BIOLOGICAL BASIS OF ANTIVIRAL DRUG RESISTANCE

- all virus populations within an individual comprised of multiple variants ("quasispecies");
- virtually all antiviral drugs can generate drug resistant variants;
- higher drug dose required to inhibit replication of virus (phenotype);
- reduced drug susceptibility encoded within viral genome (genotype);
- resistant viruses may have reduced replicative ability ("fitness") and may not persist in absence of drug.

5. WHAT DETERMINES SPREAD AND IMPACT OF DRUG RESISTANT VIRUS SPECIES WITHIN POPULATION?

- risk of resistance emerging within treated individual;
- ability of resistant virus to transmit to others;
- "fitness" of resistant virus—will it persist in absence of drug selective pressure?
- pathogenicity of resistant virus compared to sensitive virus;
- cross resistance of such variants to alternative drugs.

6. PREVALENCE OF ACICLOVIR RESISTANT HSV

Setting	Patients/Regime	Number	Method	Reference
UK	Untreated immunocompetent	0/379	Pheno	Collins, 1993
USA	Untreated immunocompetent	4/1139	Pheno	Sande (In press)
UK	Treated immunocompetent	0/420	Pheno	Collin, 1993
USA	Treated immunocompromised	7/148	Pheno	Englund, 1990
USA	HIV-ve GUM	0.1 per cent	Pheno	CDC, (unpublished)
USA	HIV+VE	7 per cent	Pheno	CDC, (unpublished)

7. EVIDENCE FOR TRANSMISSION OF HSV

Only one case documented to date.

Setting	Drug regime	Number	Detection method	Reference
Sexual contact	none	1	Phenotype/genotype	Kost, 1993

8. CROSS RESISTANCE PATTERNS OF ACICLOVIR SENSITIVE AND RESISTANT ISOLATES OF HERPES SIMPLEX VIRUS

	Penciclovir sensitive Per cent	Foscarnet sensitive Per cent
Aciclovir sensitive	100	99
Aciclovir resistant	0	75

Notes:

NB: based on vitro IC₅₀ values in Vero cells (plaque reduction assay).

PHLS Antiviral Susceptibility Reference Laboratory (unpublished).

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[Continued

9. PREVALENCE OF AMANTIDINE/RIMANTIDINE RESISTANT INFLUENZA A

Setting	Regime	Number	Method	Reference
Nursing home, USA	Treatment	3/36	Phenotype	Hayden, 1997
Children, USA	Treatment	10/37	Phenotype	Hall, 1987
USA	Untreated	8	Phenotype, Genotype	Ziegler, 1994
USA	Untreated	885	Phenotype	Heider, 1981

10. TRANSMISSION OF AMANTIDINE/RIMANTIDINE RESISTANT INFLUENZA A

Setting	Regime	Number	Method	Reference
Nursing home, USA	Prophylaxis	3/18	Phenotype, Genotype	Degelau, 1992
Nursing home(3), USA	Prophylaxis	5/10	Phenotype, Genotype	Houck, 1995
Nursing home(2), USA	Prophylaxis	6/6	Phenotype, Genotype	Mast, 1991
Families, USA	Prophylaxis	5/10	Phenotype, Genotype	Hayden, 1989

Note:

In all cases, contact with treated index case.

11. ZIDOVUDINE RESISTANT HIV IN UNTREATED INDIVIDUALS

Setting	Year	Number	Method	Reference
1° Infection, Switzerland	1989	0/5	Genotype	Perrin, 1994
	1990	1/10		
	1991	0/11		
	1992	1/10		
	1993	2/10		
	1994	2/14		
1° Infection, IVDU, Netherlands	1993	1/4	Genotype	De Ronde, 1996
1° Infection, Australia	1987-94	5/61	Genotype, Phenotype	Imrie, 1996
Drug naïve, UK	1994-96	2/35	Genotype	Quigg, 1997

12. DOCUMENTED CASES OF TRANSMISSION OF ZIDOVUDINE RESISTANT HIV

Setting	Year	Number	Method	Reference
Child-to-child, USA	1992	1	Genotype	Fitzgibbon, 1993
Male-female, sexual, UK	1991	1	Genotype	Conlon, 1994
Male-to-male, sexual, Sweden	1993	1/4	Genotype, Phenotype	Wahlberg, 1994
IV inoculation, Netherlands	1993	1	Genotype	Veenstra, 1995

13. POTENTIAL CONCERNS FOR THE FUTURE

- Long-term treatment for chronic viral infections, e.g., HIV, HBV, HCV, genital herpes;
- increasing immunocompromised population;
- availability of drugs for common viral infections, e.g., respiratory infections;
- inappropriate use of antiviral drugs, possibly through OTC availability;
- antiviral drug cross resistance against a range of drugs.

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[Continued

Examination of witness

DR DEENAN PILLAY, Head, Public Health Laboratory Service Antiviral Susceptibility Reference Laboratory, Birmingham, was called in and was examined.

Chairman

579. Dr Pillay, thank you very much for coming along. Perhaps you can, for the sake of the record, give your name and any introductory comments that you would like to make before we start with questions?

(Dr Pillay) Thank you, my Lord Chairman. I am a consultant virologist working at Birmingham Public Health Laboratory within the PHLS. I am the head of a new reference unit that has been set up by the PHLS called the Antiviral Susceptibility Reference Unit which has as its main function to put into place surveillance mechanisms and also develop an understanding of **antiviral drug resistance**. Other pertinent links I have with the area are as the chairman of the Antiviral working party of the British Society of Antimicrobial Chemotherapy.

580. Thank you. Perhaps we might now go into the questions. We have been dealing for the last couple of weeks with antibacterial resistance, a little bit with antinematodes too, but we are now dealing with antiviral resistance. What are the features which distinguish antiviral resistance from that of antibacterial resistance to antimicro-organisms?

A. My Lord Chairman, in essence the genetic basis of resistance to antiviral drugs is as for antibacterial resistance. In other words, there is a genetic basis. Where viruses differ from other organisms is that in addition to being smaller they are, in essence, just pieces of genome; they do not have any extraneous pieces of DNA such as plasmids which you would have heard about with regard to transferral of resistance. So antiviral drug resistance is encoded within the viral genome, and that is an important principle. The precise position where that resistance is encoded is in general within the gene that codes for the target of the drug. The drug will target, for instance, with HIV the so-called reverse transcriptase of the virus; there will be alterations within the genome, within that gene, there. With regard, for instance, to amantadine resistance in influenza A, there will be a mutation or a change of genome in the gene coding for the M2 protein which is the target. A slight alteration is with drugs that need prior activation within the virally-infected cells. An example here is acyclovir with herpes simplex virus, where the acyclovir needs to be activated, as it were, by one enzyme of the virus before that activated drug inhibits the second target. So there there may be mutations or alterations in the genome of either the viral thymidine kinase which is the activated protein; in the DNA preliminary, as it were, of the virus.

581. The problems of testing antiviral resistance clearly differ from those of testing antibacterial resistance, do they not?

A. You are right in a way. There are two ways of looking at resistance testing with regard to viruses. One is phenotypic testing. Phenotypic testing measures the susceptibility of the virus to drug. That is very similar to antibiotic resistance testing. One of the problems with

viruses though is that many of them do not grow, some are very difficult to cultivate in the laboratory, or they take a long period of time to grow—2, 3, 4 weeks. It is for that reason that there is now increased interest in looking at genotypic tests. These range from detection of specific base changes which we know code resistance, to sequencing large parts of the genome which will allow us to detect those mutations that are relevant. So there are two broad methods of antiviral resistance testing, both of which have advantages and disadvantages which will differ between viruses and also with regard to the reasons for testing. If it is for diagnosis then you want a quick assay and you go down one route. If you are looking at surveillance there may be alternative, cheaper methods that can be more appropriate.

Lord Gregson

582. I am somewhat concerned about the loose use of the word "mutations" as against the term "natural selection". As an engineer dealing with electromagnetic radiation, "mutation" has a very defined action which does not seem to occur in this connection. In your paper you have several times used the term "selection" rather than "mutation". Are you implying that these resistant genes exist in nature anyway, and they are only brought to dominance by the action of the antiviral drugs?

A. My Lord, perhaps I could clarify my use of the word "mutation", as it is particularly important. What I mean by "mutation" is any change at any base from a defined genome of a single virus. For instance, let us take HIV where the enzyme which replicates the genome, reverse transcriptase, has a very high error rate. For every genome that is produced from that template, for each new virus, there will be approximately one mistake, one base mismatch. That is mutation, whether it is good or bad. With viruses like HIV where you have a production rate within the infected individual of 10^9 per day, you do not have one virus within that individual. Rather there is a quasi-species, comprising many different genomes, and one of those may very well encode a change which will link to drug resistance. When you then put on a drug-selective pressure, that minority species virus grows out into the majority species.

583. In other words, it is Darwin at the speed of light?

A. Absolutely.

584. Which is not mutation?

A. It is Darwinian evolution.

Lord Jenkin of Roding

585. Can I preface this by saying that in all these matters I am a complete layman. I was the Secretary of State for Health, but this science had hardly been invented when I was there. I would find it very helpful,

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[Continued]

[Lord Jenkin of Roding *Contd*]

Dr Pillay—because this is obviously an important subject—if you could prepare for us a statement on what you have just been talking about, in language which laymen can understand. I think it is nearly there, but I would find it extremely helpful if you could do that.

A. Of course.

586. I have been left with the impression that the processes whereby viruses acquire resistance are extremely similar to those where bacteria acquire resistance. You have mentioned the point about the difficulty of growing viruses in a laboratory, that it takes weeks rather than hours, in spite of the extremely rapid reproduction phase. Are there any significant differences therefore between what happens to viruses where you obviously have a massive expertise, and the field of bacteria on which we have been concentrating?

A. There are similarities. The differences are that different classes of viruses have very different natural histories and epidemiology. For instance, with a virus such as herpes simplex—the cold-sore virus that I would say virtually all of us are infected with—if we come into contact with somebody else with that virus it is very unlikely that we will be infected by that virus, because we have already got it. The virus is within ourselves, and our immune system stops us being reinfected. So that tells us something about the potential for transmission of drug-resistant herpes simplex virus. On the other hand, there are viruses such as HIV, that I am presuming none of us are infected with, and therefore if we come into contact with a drug resistant strain, it may be that that is very, very important. So although you may feel that is not answering your question directly, what I am saying is that we cannot look at antiviral drug resistance as one, we have to look at each component part. That is the first thing. The second thing is that drug resistance may lead to a virus, which has reduced replication ability; because of its small genome—drug resistance within viruses must be coded within that bit of DNA or RNA, rather than, for instance, a plasmid. Therefore, there are many drug-resistance mutation changes which will lead to a virus that will not be able to grow, or will not cause disease. Therefore, drug resistance in viruses is not necessarily a bad thing, but we have just got to be much more critical about precisely which viruses we are talking about, their mode of spread and so forth.

Lord Porter of Luddenham

587. When we are talking about bacteria we seem to be extremely successful with drugs, with antibacterials, until resistance rears its ugly head, but I was under the impression that there are many virus diseases for which there are no drugs. This is not resistance, is it? Could you say a word about the differences between the efficacy of whatever drugs there are in the viral and bacterial worlds?

A. Am I right in thinking your question is, why are there some viruses that cannot be treated, my Lord?

588. Yes, exactly; whereas this is much less common in bacteria.

A. First of all, I think that far more is known about bacterial metabolism, and the pharmaceutical companies have invested large amounts of money in

identifying potential targets and then large-scale screening of compounds. The techniques have been available for easy screening of compounds to see if they are active against particular bacterium, because the bacteria can grow easily. With viral infections there has recently been again an enormous investment by the pharmaceutical industry, so that now there are a large number of drugs against new viral targets that are now in clinical trials. The next 10 years will see an exponential growth in licensed drugs against new targets. This is a consequence of scientific endeavour, of trying to understand how viruses work, which is more difficult than looking at bacteria, because they are small things that do not grow. The second thing is identifying new targets and developing drugs through novel chemical mechanisms to approach those. So it is a scientific lag, I would say.

Lord Winston

589. Dr Pillay, it strikes me that it might be quite useful to the Committee if you explain in brief the difference between how viruses cause disease and how bacteria do. I think that it would be quite useful to hear about their mechanism of action in the cell.

A. Unlike bacteria, viruses are obligate intracellular parasites. That is, they can only replicate inside cells, rather than having self-sustaining extracellular replication, as for bacteria. There are generally two forms of viral pathogenesis. Firstly, viruses can directly kill or alter their host cell. In essence, the cell become a virus factory. There are also a number of examples whereby the normal host cell processes are 'hi-jacked' by the virus, and thus the normal cell function is destroyed. This may not always lead to cell death. It may, for instance, lead to uncontrolled cell growth, thus generating a malignancy. This may be the cause for human papillomavirus and cervical carcinoma. Secondly, expression of viral proteins on the cell surface, or alteration of host cell protein expression may lead to an abnormal immune response. This in turn may generate disease. A good example of the latter is glandular fever (caused by *Epstein-Barr* virus). HIV disease may also have an element of immunopathology, as well as being due to direct viral destruction of lymphocytes. Thus, the major differences between bacterial and viral disease is that viral pathogenesis originates within the host cell.

Lord Dixon-Smith

590. We do so much work to control the consequences of both bacterial explosion and viral explosion in the body by producing anti-bacterials and antibiotics, would not a more fruitful source of research perhaps be in finding out how to keep the body's immune system in balance so they did not explode in the first place?

A. I agree. Vaccination—presumably you are talking about vaccination—has led to the major benefits we have seen in the world with regard to infectious disease. Smallpox has been eradicated, polio appears to be on the fringe of eradication. These are major killers and I would agree. Of course one has to ask the

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[Continued

[Lord Dixon-Smith *Contd*]

industries that develop vaccines why they choose to invest in one line compared to another. On the other hand, progress with vaccination against HIV has been very slow because we do not fully understand the nature of the immune response against HIV. Coming back to Lord Winston's question about why these things cause disease, with HIV we are still unclear about that immuno-pathology, what it is about the immune system that sometimes causes disease and sometimes protects the individual. There are other examples, hepatitis B where of course now there are highly effective vaccines, and with the implementation in those areas of the world where hepatitis B is endemic—the Far East for instance—really it is a major hope that there will be a large change in the morbidity and mortality we see in some 50 years' time. I would agree with you, prevention is better than cure and the topic of this Committee is precisely the limitations of "cures".

Chairman

591. I think we should move on to the spread and impact of resistant viruses and the relationship between primary antiviral resistance arising in the patient by viral mutation and resistance acquired by viral transmission.

A. Certainly. If I can go through my sheet number five which I think highlights the major issues: what determines the spread and the impact of drug resistance within a population? Firstly, as your question alludes to, it depends on resistant viruses emerging within an individual. That individual, while being untreated, may have a small proportion of their viral quasi species which are drug resistant viruses. If that is a very, very small proportion then the risk of transmission to person B is going to be equally small. On putting a selective drug pressure into that individual the majority of that virus that will emerge will be drug resistant. Now what determines whether that will spread to others? First to consider the mode of transmission. There are some viruses like influenza, the common cold viruses, that spread by aerosol route. What about some other viruses that we are particularly concerned about, HIV, for instance? HIV can be transmitted sexually, increasingly through heterosexual sex, it can be transmitted from mother to baby, it can be transmitted through blood to blood contact through blood transfusion or otherwise sharing of needles by intravenous drug users. We know that the quasi-species that exists in the genital tract is different from the virus that exists within the blood and may very well be different from the virus that exists within the brain. This is because the viruses need different properties within the individuals to grow in those different areas. So, that is the second point, we have to ask the question, for instance on HIV, is it more likely that sexual spread is likely to lead to resistance than transmission through other ways? The third aspect is what I call the fitness of the virus. I have mentioned that these viruses are very small, therefore many of the mutations or changes in the genome which would confer drug resistance would lead to that virus being less able to grow than the preceding 'wild type', which, after all, has evolved through natural selection into the fittest virus. By definition the virus we all have is the fittest virus that can exist in that *milieu*. So, if you take that

virus out and transmit it to person B who is not taking that drug, it may very well be that virus will not grow very well. That is another determinant. We know that is the case. We know that many drug resistant strains of virus do not grow as well as so-called wild types, so that is a factor to take into account. The next issue is whether the drug resistant virus is as likely to cause disease. For instance, Acyclovir-resistant herpes simplex virus, has a change in a gene called thymidine kinase. We now have one definite case where we know that virus has been transmitted to another person. We also know, from animal models of infection, that virus that has a deficient thymidine kinase can invade the central nervous system less well than wild type. It may be that these drug resistant mutations, although they can transmit, may be less pathogenic. These are all variables which I think will determine spread. Lastly, of course, which is very important with the increasing number of drugs we have, is whether a virus resistant to one drug, can be controlled by other drugs or is cross resistant to many anti-viral drugs. In summary those are the determinants.

592. Can we go back to the pathogenicity of resistant viruses. Is it the general status that pathogenicity is enhanced or does it depend on the individual virus?

A. As far as I am aware there is no evidence that any drug resistant viruses have enhanced pathogenicity. Drug resistant influenza, appears to be as pathogenic as the wild type. I have mentioned animal model evidence suggesting that drug resistant herpes simplex may not be so pathogenic, but really there is very little clinical evidence to support or refute that.

Lord Jenkin of Roding] Can I say that strikes one as being a completely different situation from that affecting bacteria. We have had no evidence to suggest bacteria that acquire resistance are less effective in causing disease.

Lord Perry of Walton] We have. We heard some in America.

Lord Jenkin of Roding

593. There is another parallel there which I think is very interesting. Does this suggest a line of research?

A. It is essential to know whether a drug resistant virus is likely to be more or less pathogenic. We have some of the means to study this before drugs even come to be licensed.

Baroness Platt of Writtle

594. Can you describe the systems in place in the United Kingdom for monitoring antiviral resistance, particularly the PHLS Antiviral Susceptibility Reference Laboratory in Birmingham?

A. Certainly. This is a subject in its infancy and, as I mentioned, the PHLS Reference Laboratory was set up last year. As far as I know this is the only one of its kind within the world. There are many laboratories which are undertaking research on drug resistance, research on specific viruses, but as far as I am aware there is no dedicated laboratory to set up surveillance systems on a national level. We are in the process, therefore, of

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[Continued]

[Baroness Platt of Writtle *Contd*]

setting up those systems but this is not straightforward. In addition to the surveillance mechanisms required to acquire viruses, which we are fortunate within the United Kingdom the PHLS does provide, we need techniques that we can use on a large scale to test for resistance. Few assays currently available have been validated. Outside of small groups that have evaluated techniques for specific projects there is little national or international consensus on breakpoints which determine whether a virus is sensitive or resistant. All these techniques are very expensive at the moment. We feel that one of our first priorities is to establish these techniques before we put into place and start active surveillance. Having said that, the herpes simplex drug resistance assay is probably one of the more validated assays and currently we are undertaking a survey of all herpes simplex isolates from immuno-compromised patients from sentinel laboratories around the United Kingdom. We are also looking at the susceptibility of these viruses to a range of other anti-herpes drugs. We are also developing our surveillance strategy for HIV drug resistance.

595. So have you yet acquired enough data?

A. No. Your question also alluded to other things going on in the world. I know of a couple of other surveillance studies that are currently trying to be set up. One is run by CDC in Atlanta, the Centre for Disease Control. They are currently trying to develop a protocol for herpes simplex and resistance. This is a very large proposal involving testing some 4,000 to 5,000 isolates from selected centres within the US each year. The cost of that is estimated at, we would say, some £50 to £100 per assay, which is astronomical. We all need to secure funding. The CDC have also initiated a study of transmission of HIV drug resistance, that is, looking at specific groups of patients and collaborating with a European AIDS epidemiology network which is based in the Netherlands. They are discussing protocols but as far as I know, no data has yet accrued.

Lord Gregson

596. Is herpes simplex virus in the wild state all the same, is it a standard virus? I am not talking about resistance. Is it site specific in effect?

A. Herpes simplex is classified into type one and type two. Type one in general causes cold sores, type two in general causes genital disease.

597. They are two different viruses.

A. The genomes of herpes simplex viruses split into two groups, although within each type, many different species can exist.

598. But one and two are well defined different viruses?

A. Yes.

Lord Walton of Detchant

599. Could I follow up on that question just to ask you a question which may be based on outdated knowledge. The herpes simplex virus type one causing cold sores may on rare occasions produce a fatal

encephalitis. Nobody quite knows what it is that causes that change in the activity of the virus. The question is whether the fact that Acyclovir can be bought without prescription for the treatment of cold sores is likely to have any potential influence on making herpes simplex encephalitis more prevalent?

A. Firstly, the precise biological basis of why the virus reactivates remains unclear. I am unaware of any information which would suggest that drug resistant virus is any more likely to cause encephalitis. As I said before, I think the opposite may very well be true. On the other hand, you raise the issue about availability of drugs. There is no doubt that there is the potential for widely used drugs to change the virus in ways we are currently unaware of and which then may alter the pathogenicity of that virus.

Lord Perry of Walton

600. The infecting bacteria that a patient gets often does not have a resistant strain already there. As far as I can make out from what you have been saying nearly all virus inoculants are a mixture of strains that could be resistant.

A. Yes.

601. Are we not in a situation that whereas you have got to develop drug resistance in a bacterial inoculation you are very much more likely to develop it in a virus because it is there already; it does not require a change to occur?

A. Yes.

602. Are we not bound to get resistant strains to every antiviral that is produced? Are they ever going to be seriously available for long enough to make a difference?

A. You are right that resistant virus is there already and you select out. On that point, firstly, it may not be the case. For some viruses that have a single mutation, a single change in their genome that causes resistance then they are going to be there all the time. There are some viruses, and again I come back to HIV which we know most about, that need four, five or six mutations, not just one, to cause resistance. The chance that these viruses spontaneously develop is obviously less, and they will evolve from an initial one or two mutation virus, with sequential acquisition of mutations. The point you make about the lack of efficacy of drugs is absolutely right. A good antiviral agent almost by definition will generate resistance. In fact, if a drug causes resistance, it suggests that is not working as a specific antiviral drug. The next question then, is how we can use these drugs well? For many viral infections, it is clear that the risk of emergence of resistance is reduced, the more that viral replication is reduced. This demands appropriate use of drugs. I, and I do not think anyone else in the antiviral field, would ever say you can have a scenario where resistance never occurs. I think the clinical impact and public health impact is determined by how we use those drugs.

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[Continued

Baroness Platt of Writtle

603. In monitoring antiviral resistance, how can you ensure that the prevalence data obtained is accurate? In particular, how can you obtain meaningful denominator information?

A. As I mentioned in response to your previous question, we are really in the infancy of surveillance for these viruses. I would stress that we need to ask different questions of the different viruses. For instance, for herpes simplex virus resistance almost only occurs in patients who are immuno-compromised. We do not have the resources to look at the whole population. We have got to be realistic about that. That would determine how we would target our surveillance. I have got some calculations here which may be useful. If we assume in the immuno-competent population, a prevalence of some 0.3 per cent of drug resistant herpes then if we are going to develop surveillance to look at changes over time, then we have got to be testing 3,500 isolates a year. This will cost something like £100,000. We now have to be realistic about what is achievable.

604. Realistic in money terms?

A. Yes, and how to get the best information out of the resources that we have. Continuing surveillance for drug resistant HIV demands a different approach. We need to stratify patients and, again, the more stratifications you have which determine your prevalence of resistance the more patients you need to enrol. We need to look at the geographical pattern within the United Kingdom, for instance. We know there are more drugs used and more drug trials being undertaken in some of the big London centres than some small centres outside London. Is that going to determine the emergence of resistance and the transmission within those patient groups and those communities? There is also the change in risk group. Earlier I alluded to the fact that in patients who may be infected through the intravenous route, whether they are haemophiliacs or whether they are intravenous drug users, resistance may emerge or may be transmitted to a different extent from those who are infected sexually. We have to stratify by risk group. There is also age and there is also the level of immuno-suppression. All I can say is these are issues we are currently discussing. I must say I think the more there is an international effort in this then the better.

Chairman

605. Are you able to tell us the budget of your reference lab in Birmingham?

A. The budget of the whole lab is in the ball park figure of what I suggested would be the cost of just surveying herpes simplex virus isolates for one year.

606. £200,000 a year?

A. Or less.

Lord Jenkin of Roding

607. If I have drawn my conclusion right, there can be no question of making any of this notifiable?

A. No.

608. It is just overwhelming.

A. Exactly.

609. In relation to bacteria, certain of the more common bacteria, the MRSA's and so on, there have been quite strong suggestions that the mechanism of making the conditions notifiable would be a step forward.

A. On the other hand, what I have tried to highlight is that we are still unclear what the clinical implications of drug resistance are, they are different for different viruses, and currently, unlike antibacterial resistance testing, antiviral resistance testing is not available, there would be very, very few laboratories which are capable of doing this.

Lord Dixon-Smith

610. Just considering the practicalities of notification, is there not also a problem because in all too many instances precise records are not kept of what the problem is and what the treatment is? If the records were accurate then surely if you could access some of the problems—I would not say they would be diminished—you could have some facts on which to base the studies?

A. I absolutely agree, and that is why when we are developing our structured surveillance of looking at certain centres and enrolling their patients into this study, one of the key aspects is to have full documentation on those patients. Something similar happens with, for instance, influenza surveillance which occurs every winter, in which specific general practices are targeted for acquisition of viruses from patients with respiratory illness. There is good documentation there. That is different from the scenario perhaps with antibacterial resistance with the widespread acquisition of data which may or may not be useful.

611. The next point is this question of the developing of knowledge. If we had seen the problems of antibiotic resistance back in the 1940s it is possible that we would have done something different by way of the development of antibiotics and, more importantly, in their use. Do you have concerns for the future of antibiotics? Have you thoughts on the strategy for their development and their use in this country in order to minimise these sorts of resistance problems?

A. I think this is probably the key area for me. As antivirals come into the marketplace we need to be protocol driven and those protocols need to be evidence based. In my view clinical virologists are essential for that within a hospital setting as well as in primary care. At the moment antivirals are predominantly used within patients who are likely to generate resistant virus. Antivirals are predominantly used within hospitals, in immuno-compromised patients. There should be protocols for the use of antivirals which, as I mentioned, should be evidence based. I think, number two, there should be clear diagnostic criteria for using antivirals. We have all seen what has happened with antibiotics whereby they are often prescribed with little evidence of bacterial infection. This is part of our goal within the British Society of Antimicrobial Chemotherapy which is now working to try and develop these protocols and respond to new drugs as they emerge. The third aspect of care is clearly related to over the counter drugs. Currently the over the counter drugs available are

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[Continued]

[Lord Dixon-Smith *Contd*]

topical treatments for cold sores. The evidence to date is that there is a very low incidence of resistance in patients treated for that. However, I am certainly aware of many strategies that the pharmaceutical industry have for trying to push new therapies over the counter. I think there needs to be surveillance data on resistance before these drugs actually get licensed for over the counter use. I would also argue that there should be sufficient research, a full portfolio of research undertaken, to ask precisely these questions: what is the risk of emergence of resistance and the transmissibility associated with that?

Lord Perry of Walton

612. Can I ask a question going back to the inocula of mixed viruses. Is there not a case for always treating with two or three different antivirals in order to prevent resistance happening? They do this in things like tuberculosis and I know they do it for HIV.

A. Yes.

613. Is there not a general case on that basis?

A. I think as a principle, treating a viral infection with drugs which target different sites of viral replication will be more effective and reduce the risk of emergence of resistance. We have learnt that with HIV and TB. Currently, even with hepatitis B, we already know—and the drugs have not even been licensed yet—there is something like a 15 per cent risk of emergence of resistance after one year with monotherapy. Here again, combination therapy will be the key. Of course, clinical trials of drug combination means the pharmaceutical industry agreeing to trial combinations of “competing” drugs.

Lord Dixon-Smith

614. There was some evidence that the use of combination, whilst it was initially very successful, did lead to resistance and more importantly there was the potential abuse of the use of antibiotics in the sense that once they got the precise definition of what they were treating and could go back to one antibiotic all too often they did not; they carried on with the two, which was unnecessary.

A. In that sense I do think there are lessons to be learned. I must say that it is still possible to get viruses that are resistant to a whole range of drugs. We now have HIV species that are resistant to five drugs, that has been isolated. Because of the nature of viral fitness that I mentioned before, there is a theoretical possibility that if you then take the drugs away, the virus reverts back to drug sensitivity over time.

Lord Jenkin of Roding

615. How long could that take? There must be many variables.

A. We are talking about case reports so it is very difficult to generalise.

Lord Porter of Luddenham

616. You said in an article that you wrote in the BMJ that you felt antivirals would be as important by the beginning of the next century as antibiotics over the

last half a century. Does this mean in your mind that they will become as affordable and as easy to use as antibiotics?

A. Antibiotic use started with treatment of life threatening diseases. Then over time there have been more antibiotics available for treating perhaps less severe infections, with less rigid criteria for their use. Now, of course, we are in a situation where patients demand antibiotics when they go to their general practitioner. That is the way things have come along. Obviously within that context there have developed “affordable” drugs. Where are we with antivirals? Antivirals perhaps require more investment, especially nowadays in the pharmaceutical industry and certainly the industry is demanding a reasonable return for its investment. Currently we are limited to treating viruses that cause considerable disease. For example immuno-compromised patients who get severe herpes simplex or other herpes virus infections, HIV, hepatitis B which again can cause considerable morbidity, and influenza which can be a killer as well. In addition, longer term treatment is given to patients with recurrent genital herpes, in order to reduce recurrences. Major changes will occur in the future with the development of drugs against other viruses, for instance the papilloma viruses, the wart viruses, and the common cold virus. In other words, we are moving to viruses that are not life threatening, but cause discomfort. In terms of the population's expectation for increasing health then it seems that treatment will be given for less severe infection. These drugs may also be easier to take—for instance, topical treatments and inhaled drugs for respiratory infection. In this sense I think we are moving towards what we are currently seeing with antibiotics. By definition, these common viral infections are also very transmissible. Thus, we must be concerned about the potential spread of resistance.

Lord Gregson

617. It seems we are moving much quicker on the antivirals and now we have got antivirals over the counter but we have not got antibiotics over the counter yet. Do you think this is a trend? Is it getting much worse?

A. Having over the counter antivirals?

618. We have antivirals over the counter now.

A. I must say they are very, very limited. Of the array of—

619. You have not got any antibiotics over the counter.

A. There are topical treatments and so forth.

Chairman

620. In terms of over the counter compared with this country, what about other countries? In some countries in the European Union you have over the counter antibiotics in profusion. What is the situation with antivirals?

A. Starting with the United States, which is perhaps harsher than others, there is great resistance to having over the counter antiviral drugs. France and Austria

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DR DEENAN PILLAY

[Continued]

[Chairman *Contd*]

have over the counter anti-herpes treatments. Within Britain there already is over the counter treatment. There are variations between countries.

621. Do they pose a danger, do you think?

A. I think at the moment, as I mentioned, the sorts of drugs that are currently available over the counter probably do not; however, surveillance needs to be done. Certainly given that there are differences between countries, and I am particularly considering the anti-respiratory virus drugs, there may be some concern.

622. Do you think there will be a major resistance problem if there should be an influenza pandemic? The news just recently from Hong Kong would cause us to have concern, especially with respect to the speed at which resistance seems to arise.

A. My Lord Chairman, I think there should be concern with a pandemic strain of flu, in other words a strain of flu against which current vaccines will not protect and where, therefore, antiviral drugs become the only line of defence. Currently available drugs rapidly lead to resistance. The limitation of current drugs, of amantadine, or rimantadine which is another form, against influenza is that it is only active against influenza A. The benefit of newer drugs is that they are active against influenza A and B. As I mentioned, both of them generate resistance. There are two ways in which drugs would be used in a pandemic environment. One would be to treat those individuals who were at risk of severe morbidity and mortality. The second would be as prophylaxis, to protect groups of individuals against the disease. Examples are health care workers and high risk patients who, if they got influenza, may be at risk. Spread of resistant virus is most likely in situations where treatment of disease and prophylaxis occur together. This becomes a logistical problem within a health care setting. When patients are coming in, for instance, those who are being treated will need to be kept separate from wards where the staff are being treated prophylactically to keep them working. Yes, there will be a problem.

Lord Porter of Luddenham

623. I would like to ask a quick question about research and particularly the funding of research. Is this a rather exceptional field in the sense that the power of the AIDS lobby is going to make funding less of a problem than in most areas?

A. Of the major research sources within the United Kingdom, the Medical Research Council did have an AIDS Directive programme earmarked for AIDS, but that has been disbanded and now AIDS competes with other areas of infection and physiology, I think it is well recognised that it is extremely difficult to get HIV funding now through the MRC. The Wellcome Trust does not fund AIDS research. The Imperial Cancer Research Campaign and Cancer Research Campaign do not fund research on HIV therapy *per se*.

624. Can I just chip in to see if I am understanding this: is that a result of the funding which is available elsewhere from the AIDS lobby?

A. I am unaware of the history of the Wellcome Trust's position and I do not know whether that was

because of the fact that the MRC in the late 1980s developed a targeted AIDS directed programme or whether it was because of something else, at the time the Wellcome Trust was linked to Burroughs Wellcome. I am not aware of that. The reality now is that for four or five of the biggest research funders within the United Kingdom, it is very, very difficult to get money for HIV research.

Lord Winston

625. You said that ICRF do not fund viral research programmes; that is not strictly true, is it, because a lot of the ICRF units are doing related work in the field of virology?

A. They are but not pertaining to HIV target resistance.

626. Not HIV.

A. I was talking about HIV.

627. Viruses which react to cellular abnormalities?

A. No, I was talking about HIV because the question was in terms of the AIDS lobby. Research into basic mechanisms of viruses is going on apace, of course, funded by the MRC, Wellcome Trust and all the cancer charities.

Lord Jenkin of Roding

628. I was until recently Deputy Chairman of the ICRF and this precise question came before the Council when it appeared that some of the work that was being done in the ICRF laboratories was of direct relevance to HIV. It was explained that if you go back to looking at the fundamental nature of viruses and indeed of the genomic make-ups, of course much of the work will be relevant to a wider field of research. We were completely satisfied that we were not misleading our donors when we were asking for funds for cancer research and some of the work was relevant to the others. Perhaps you would not like to comment but it seems to me that if there is indeed a substantial flow of research money which has been sparked off by the public interest and concern on HIV, surely this must lead to a steady broadening of knowledge of all mechanisms that you have been talking about in relation to a whole range of viruses, or is that not the case?

A. Sorry, your question is whether that interest in HIV has had a spin-off with other viruses?

629. You have put it much more clearly than me!

A. You are absolutely right but this research is outside the HIV resistance field, which I was alluding to, which is perhaps a difficult area to get funding, I think these basic mechanisms that have been looked at really pertain to all resistance because we are talking in essence about viral variability, the broad area of resistance comes within viral variability, the vaccine development that is associated with the relationship of viruses with cancer and interactions with immune systems so I would agree with you. It is far more difficult to obtain funding for more targeted research or funding to try and support the surveillance that we have talked

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DR DEENAN PILLAY

[Continued]

[Lord Jenkin of Roding *Contd*]

about, developing techniques which again I mentioned was key to undertaking this.

Lord Walton of Detchant

630. Leaving aside the question of HIV, the fact that there are several malignant processes like Kaposi's sarcoma, Burkitt's lymphoma and various forms of leukaemia which are due to viral infection, surely it is proper that some cancer money should be spent on investigating them? The second question is whether, since the MRC has given up awarding project grants to concentrate purely on programmes and units, it has become more difficult to get funding for viral research?

A. With regard to the first question, all I can say is I wholeheartedly agree with you that the lessons which can be drawn from viral causes of cancer may very well be pertinent to drug therapy and viral variation although together with many others I find myself putting in grant applications to try and bring in this area of research under another guise. On the second aspect, with regard to the new MRC regulations, I think many of us in

academia are struggling currently with what does a grouping mean, how can we put this forward to the MRC and so forth. I wait to see how successful we are.

Lord Winston

631. Some of the areas you are specifically involved in seem to me to be appropriate for the R&D arm of the NHS, what is the situation there?

A. This is somewhere where we have been more successful at attracting funding.

632. Are you reasonably hopeful on the R&D arm in general?

A. I am aware of the new structures in place certainly and then more specifically I can talk about the West Midlands where there is quite a high profile attempt to rejuvenate and have a more rational approach to awarding grants. As I say, recently we have been awarded a grant which was quite a speculative project. The point is to pump prime. At the moment I am feeling quite hopeful.

Supplementary Memorandum by Dr Deenan Pillay

THE BIOLOGICAL BASIS OF ANTIVIRAL DRUG RESISTANCE

Viruses comprise nucleic acid, either RNA or DNA, tightly bound to protein. They may also have a lipid envelope acquired from the infected host cell. Viral genomes are small, compared to bacteria, and do not encode all proteins necessary for full replication. Therefore they require host cell proteins to reproduce, making viruses "obligate intracellular parasites". Replication cannot occur outside the cell, although some viruses are robust enough to survive for hours or even days outside a host. Thus, viruses are fundamentally different to bacteria, which are self replicating organisms.

The natural history of human viral infections can take three general forms:

- (a) Acute infection: a susceptible individual (lacking appropriate immunological protection afforded by previous infection, vaccination, etc.) becomes infected, which may or may not cause symptoms. Within a few days, a vigorous immune response develops, which clears the virus. The individual is subsequently immune to re-infection with the same strain of virus. Examples of such infection include measles, mumps, rubella, influenza. Some viruses, such as influenza, undergo rapid genetic variation over time, leading to alterations in their protein structure. In these cases, pre-existing immunity may not protect against a subsequent variant, and "re-infection" can occur.
- (b) Chronic infection: although an immune response occurs to all new infections, some are unable to clear the body of infection (e.g. antibodies do develop but these are "non-neutralising"). In such instances, infection becomes persistent, and usually the virus can be detected over a long period of time, often for life. Examples of these infections are HIV, hepatitis B and hepatitis C. In all these cases, persistent viraemia (virus in blood) occurs, in concentrations up to 10^9 virions/ml of blood. When an individual is immunocompromised, for instance due to HIV infection, following transplantation or during cancer chemotherapy, infections which are normally rapidly cleared (acute infections) can become persistent because of the inadequacy of the immune response.
- (c) Latent infection: in these cases, acute infection (again, symptomatic or asymptomatic) is followed by the establishment of non productive infection in specific host cells. In other words, the viral genome persists within a cell without production of virus. "Reactivation" of virus from these latently infected cells can occur at any time in the future. Examples of these group of viruses are herpes simplex virus (cold sores and genital herpes) and varicella zoster virus (acute infection causes chicken pox, and reactivation leads to shingles). The immune system plays an important role in limiting reactivation—thus, the immunocompromised are at risk of severe disease due to reactivation of these herpes viruses.

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[Continued

Antiviral drugs target specific viral proteins essential for effective replication. These drugs may also be first activated by other viral or cellular (host) enzymes. Resistance to these drugs is usually encoded within the viral genome, leading to production of altered enzymes which are not inhibited by the drug in question. Of course, these drug resistance changes must not compromise the ability of the viral protein to carry out its normal function, otherwise the drug resistant strain will be replication incompetent (reduced "fitness").

Viruses replicate at a very fast rate—thus, the half life of HIV in plasma is one day, and this is little different for hepatitis B. For each viral genome replication cycle, there is a finite risk of errors being introduced into the progeny genome i.e. a base which is not complimentary to the parent genome. The risk differs between viruses; the viral polymerase of HIV (reverse transcriptase) has a high error rate of $\sim 10^{-4}$ /base. Thus, for each 10,000 bases, one mistake will occur, leading to an altered amino acid sequence with respect to the parent. This risk is lower for herpes viruses since viral DNA polymerases contain "error-correcting" activity. With some 10^8 HIV virions produced each day, it is therefore not surprising that the viral population within an individual is a highly heterogeneous in a genetic sense. This is known as a quasispecies. All viral populations will, to a greater or lesser extent, be a quasispecies, rather than a homogeneous population. If antiviral drug resistance requires just one amino acid alteration from "wild type", then it is highly likely that this particular genome (with one base change) will already be represented within the quasispecies, albeit at very low frequency. In true Darwinian fashion, once the drug selective pressure is imposed, this virus will preferentially replicate (other viruses will be more sensitive to inhibition by drug), and become the majority species.

Antiviral drug resistance is most well understood for HIV. A large number of mutations, or sets of mutations are associated with resistance. The ease with which resistance occurs depends somewhat on how many mutations are required to confer this property on the virus. As highlighted above, single mutations, (compared to the parent), will already exist within the population. If four or five mutations are required however, it is statistically less likely these will emerge spontaneously, and they will need to be acquired sequentially i.e. one after the other.

The number of mutations required for resistance is not the only determinant of resistance emerging. Perhaps most important is the degree to which viral replication is suppressed by treatment. If viral replication is inhibited by 100 per cent, it is more difficult for resistance to emerge, especially if multiple mutations are required. This can be diagrammatically represented by the so-called "bell-shaped curve" (Figure 1). It is also true that viruses with a very high replication rate within the body as a whole, such as HIV, hepatitis B and hepatitis C will generate drug resistant mutants at a faster rate than viruses with lower replication rates.

It is evident that the majority viral species within the quasispecies has evolved to be fittest—the best replicator—within its environment. Since the viral genome is utilised very efficiently, with no extraneous gene material, it is unsurprising that mutations causing drug resistance will also impact on other aspects of the virus, including overall replication capacity, leading to viruses with a reduced replication competence compared to "wild type". Of course, in the drug environment, the resistant virus is "fittest", however, in the absence of drug it will be less fit. This is important when considering the transmissibility of drug resistant viruses, and their ability to cause disease in an untreated individual. On the other hand, it is now becoming clear that some mutations associated with drug resistance do not actually cause resistance, but rather "compensate" for the loss of fitness consequent on the resistance mutation, thus generating a virus which can compete with wild type. The risk of transmission and spread of drug resistance viruses is therefore a real one, and requires close monitoring.

Many of the concepts described above have emerged only recently, in the light of biological and mathematical analysis of HIV drug resistance. Although the constraints on development of drug resistance differ between the virus groups, the principles of antiviral drug resistance remain similar. Ascribing precise risks for emergence and transmission of resistant viruses awaits more hard scientific data.

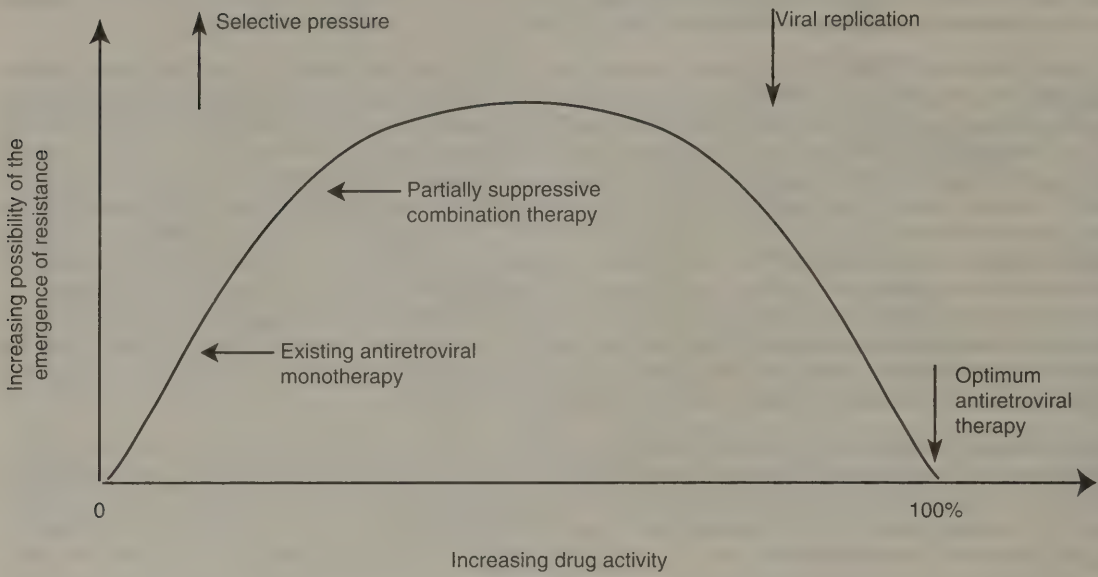
Deenan Pillay

Head

PHLS Antiviral Susceptibility Reference Unit

University of Birmingham and Birmingham Public Health Laboratory.

8 January 1998



Graph taken from HIV drug resistance and its implications for antiretroviral treatment strategies

Authors: Douglas Richman and Schlomo Staszewski

Published by International Medical Press

TUESDAY 16 DECEMBER 1997

Present:

Dixon-Smith, L.	Porter of Luddenham, L.
Jenkin of Roding, L.	Rea, L.
Masham of Ilton, B.	Soulsby of Swaffham Prior, L.
McFarlane of Llandaff, B.	(Chairman)
Perry of Walton, L.	Winston, L.
Platt of Writtle, B.	

Memorandum by Dr H McGavock

UNDERSTANDING THE IRRATIONAL AND UNNECESSARY USE OF ANTIMICROBIALS
IN GENERAL PRACTICE

CONTENTS

1. The Drug Utilisation Research Unit, Queen's University, Belfast
2. The problem of uncertainty in general practitioner diagnosis
3. Prescribing as a behaviour rather than a scientific response
4. The power of marketing

1. *The Drug Utilisation Research Unit, Queen's University, Belfast (DURU)*

This unit was set up in 1990 funded by the Department of Health and Social Services, Northern Ireland and at their request, to investigate the phenomena underlying general practitioner prescribing. The unit comprises two full-time research medical officers, one full-time statistician/epidemiologist, one full-time pharmacist, one full-time computer scientist and three clerical support staff. It receives full prescription pricing data and practice data, monthly, for all general practices in Northern Ireland from the Central Services Agency (the Northern Irish Prescription Pricing Authority). DURU has devised a variety of techniques to interrogate these data so as to reveal trends and test hypotheses regarding general practitioner prescribing. In addition, the Unit conducts more detailed research on representative samples of practices, including most recently, a large scale investigation of the relationships between diagnosis and prescribing in general practice. Unit staff also produce educational material for general practitioners and lecture widely to general practitioners throughout the province on rational prescribing. Examples of this educational material, relevant to the sub-committee's investigations are coffee table leaflets produced in 1992, encouraging doctors to rationalise their antimicrobial prescribing. The Unit has produced and published the Practice Formulary whose last three editions have been adopted by the Royal College of General Practitioners, London as its formulary exemplar, in which detailed antimicrobial guidelines are regularly updated. Finally, DURU produces COMPASS, an interrogated feedback of every general practitioner's monthly prescribing, comparing what the doctors actually prescribed with best evidence-based practice. COMPASS is taken to every practice at least annually by the Area Prescribing Advisers, for detailed discussion but fundholding practices often request this document quarterly, to drive their cost-effectiveness efforts. COMPASS has saved over £11 million in Northern Ireland, in the past three years, but could save up to £25 million annually, if fully utilised, with a striking improvement in the quality of medical treatment. The latter saving would constitute 15 per cent of the annual GP prescribing cost.

2. *Uncertainty in general practitioner diagnosis*

It is impossible to understand the irrationality of much general practitioner prescribing if one is unaware of the difference between the hospital environment and that of general practice, with respect to diagnosis. Hospital doctors are concerned with achieving certainty of diagnosis in every patient they see, whether in-patient or out-patient. Consequently, they are often in a position to use drugs precisely, whether or not they always do so. The situation is very different in general practice. The GP spends most of his or her day *managing uncertainty*. It is true that a proportion of patients in general practice have accurately diagnosed chronic conditions, such as diabetes, asthma, heart disease, benign, peptic ulcer, schizophrenia, etc. But the majority of patients consulting the GP have either short-term, self-limiting illnesses or have the vague presenting symptoms of the early stage of something more serious. The patient who is "tired all the time" could have the rare condition known as Addison's Disease but is a great deal more likely to be depressed, anaemic, hypothyroid, recovering from influenzae or to have no underlying pathology whatever! General practitioners develop the remarkable skill of managing uncertainty and assessing *improbability*. Much of GP therapy is therefore based on a diagnostic formulation in which the doctor's past experience and knowledge of the patient play a large part. It follows that

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[Continued

absolute precision in GP prescribing is probably unattainable. This means that a proportion of GP prescribing is appropriate. In such cases, the patient does not receive the medication's benefit but is subjected to its risks. Fortunately, the pharmaceutical industry has provided us with drugs which are not only extremely effective but very safe, with high benefit:risk ratios. Because of that, even if the provisional diagnosis is wrong and the prescription inappropriate, the patient rarely comes to harm but scrutiny of reports from the Committee on Safety of Medicines over the past 20 years reveals on a national basis how many patients *are* harmed by the drugs prescribed. There is an aesthetic dimension too: as highly educated men and women, GPs should surely be deriving satisfaction from the daily application of scientific principles, for prescribing should ideally be an applied science. In the case of antimicrobials there is little excuse for such presumptive prescribing. Every GP in the UK has open access to bacteriological laboratories which can supply scientific evidence of bacterial infection together with the appropriate antibiotic, usually within three days. Most infections in general practice are not so serious as to require immediate broad-spectrum antimicrobial therapy. Indeed, evidence is accumulating that where bacterial infection is present, a delay in antimicrobial therapy of 48 to 72 hours, permitting the body to mount its own immune response, often results in more complete resolution of the infection with greatly reduced likelihood of recurrence. In the case of upper respiratory tract infections, by far the commonest infectious diagnosis in general practice, most doctors are aware that 70 per cent of cases are viral in origin and will not respond to antimicrobial therapy. Yet a recent DURU survey of 21,400 patient encounters revealed that for acute upper respiratory infections (70 per cent viral in all age groups) over 80 per cent of patients were prescribed an antimicrobial *including 70–80 per cent of patients not actually seen by the doctor*. Even where the diagnosis was coryza (the common cold), 42 per cent of patients were prescribed an antimicrobial. When asked to justify such prescribing, doctors in Northern Ireland gave similar reasons to those enunciated some 10 years ago by Professor A. M. Emerson, a leading British microbiologist:

1. "I have done it for the past 20 years".
2. "Just in case".
3. "To prevent secondary infection (in a viral illness)".
4. "It relieves my worry—I feel I have done everything possible".
5. "Antibiotics do no harm". (Despite 20 antibiotic deaths annually in the UK and thousands of hospital admissions for serious antibiotic adverse drug reactions).
6. "The patient or mother demands it".

3. *Prescribing is a behaviour rather than a scientific response*

As already stated, prescribing ought to be the response of a clinical scientist to a diagnosis or symptoms or both. In fact, the past seven years' research in Belfast has demonstrated that prescribing, which may have started in the doctor's hospital years as an applied scientific activity, is modified and distorted in general practice by a wide variety of factors over many of which the doctor has only limited control. As in all behaviour, the individual is unaware or only partially aware of the influences which mould his or her behaviour. As a result of the past seven years' research, DURU has produced what we call "the prescribing jigsaw". A copy of this is enclosed on which the asterisks indicate those factors which DURU has so far quantified, Figure 1. The size of our samples and the statistical rigour with which this work has been done leaves little room for doubt as to the reliability of this work for the purposes of planning for future improvement by the profession and its administrators. (Copies of our peer-reviewed articles in the scientific literature can be supplied if required.) We have no doubt that antimicrobial prescribing is a behaviour driven by all these factors, including those which we have not yet investigated, particularly the use of drugs as symbols.¹

4. *The power of drug Marketing*

DURU's research has shown that the two most powerful influences on GP prescribing are the demography of patients on a practice's list and marketing of new drugs. In the case of antimicrobials, over the past 30 years, the drug industry has done splendid work in producing molecular variants of existing antimicrobials, superior in spectrum to previous drugs. Those suitable for general practice have had an acceptable safety record, can be administered orally, are effective for most GP bacterial infections and when marketed, have little or no bacterial resistance. Given this excellent drug profile, there is nothing to prevent a GP from adopting each new antimicrobial if persuaded that it represents superior treatment for the patient. Having spent many millions in its development, a drug company has a responsibility to its shareholders to market such drugs as enthusiastically as possible. Modern drug marketing is conducted with strategic and tactical planning which would be a credit to any modern army! Large sums of money (about 24 per cent of annual sales income) is spent on drug marketing

¹ Since DHSS (NI) has withdrawn financial support for DURU from 28 February 1998, it is unlikely that these factors will be researched further.

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and most GPs receive “drug detailing” visits from drug firm representatives four to five times per week. By contrast, Area Prescribing Advisers visit perhaps once or twice annually and postgraduate education devoted to antimicrobial therapy is a rare event. The principles of bacteriology and antimicrobial treatment are therefore pushed further and further into the background, the benefits of older, narrow spectrum antimicrobials are forgotten and the new drugs are adopted. Nor is this phenomenon confined to antimicrobial drugs. The enclosed graphs show how similar are the effects of marketing on broad spectrum antimicrobials, acid-suppressant (anti-ulcer) drugs, new antidepressants, ACE-inhibitors (heart drugs) and lipid-lowering agents (Figures 2–6). Like antimicrobials, DURU has quantified evidence that a substantial proportion of these other drug groups are also poorly targeted. Note the seasonal variation which is peculiar to the antimicrobials—upper respiratory infections peak in Winter (Figure 2).

CONCLUSION

It is hoped that this short paper has given Your Lordships a basic but reliable understanding of the phenomena underlying antimicrobial use in general practice. The question you will no doubt be addressing is “What can be done?” Because we are dealing here with a unique class of drugs whose efficacy decreases as the volume of their use increases by the development of bacterial resistance, we are considering a limited human resource similar to coal, oil and natural gas, which once exhausted, is gone forever. Increased levels of undergraduate and postgraduate education in antimicrobial use are of course important but having spent some 17 years attempting to promote rational drug use in one small region of the UK, it is my considered opinion that if this limited human resource is to be preserved for future generations, some form of statutory control on antimicrobial prescribing is urgently needed. I do not believe that self-regulation will be effective enough to save medicinal antimicrobials. Statutory control would have to include such basic principles as an imperative to conduct proper bacteriological tests before prescribing whenever possible, imperative editing of test results by laboratories, (to exclude newer antimicrobial agents from their reports, whenever older, narrower spectrum agents are effective), and a requirement to submit bacteriological results with the prescription, before a community pharmacist is legally permitted to dispense a newer, broad-spectrum antimicrobial. Of course, in cases of critical infection (rare in general practice) doctors must be authorised to prescribe presumptively. Such a suggestion will be subject to many criticisms from several quarters, including the extra workload imposed on bacteriological laboratories and the effect on drug industry profits. But if we are to preserve the antimicrobial era, the extra cost now will be more than justified, compared to the human and financial cost of the morbidity and death that were the norm before antimicrobials were discovered.

H. McGavock, BSc, MD, FRCGP

Director

Drug Utilisation Research Unit

Queen's University, Belfast

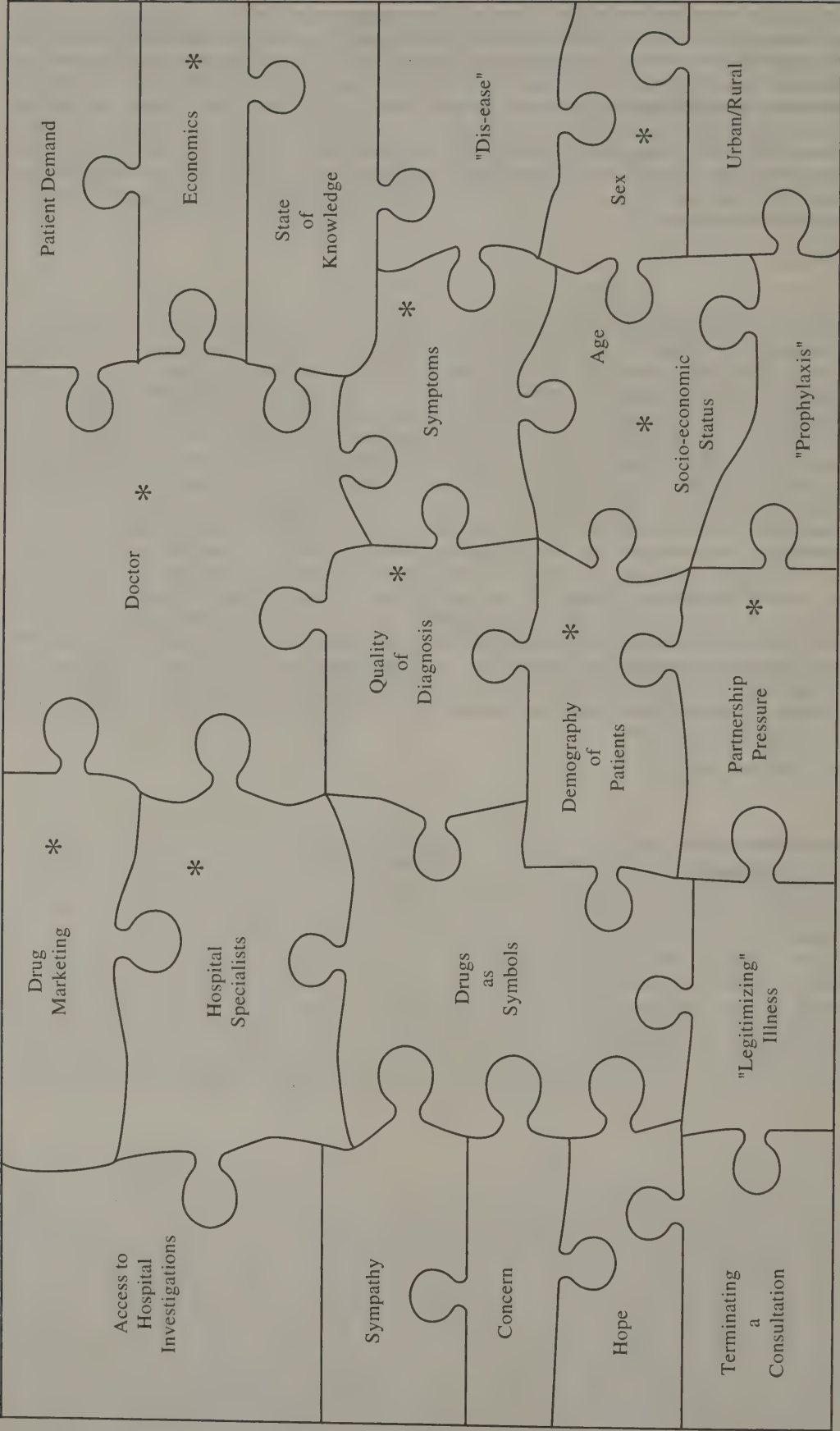


Figure 1: The Drug Utilisation Research Unit (Belfast) Prescribing Jigsaw

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[Continued

**Notes from Professor J C Petrie CBE, Head, Department of Medicine and Therapeutics,
University of Aberdeen**

I enclose an outline of some of the activities which have been developed in Grampian, in Scotland and with WHO to improve prescribing practices. These should be relevant.

In summary information which is to be implemented locally must be multi-professionally developed, valid and valued, evidence based and derived from robust systematic reviews of the literature. GOBSAT GOOD OLD BOYS SAT AT TABLE development is no longer acceptable. Local translation and relevance i.e. "ownership" must be secured through local leadership and quality assured implementation strategies linked to some locally agreed system of accreditation or "kitemarking".

APPENDIX 1

Scottish Royal Colleges Intercollegiate Guidelines Network (SIGN)

Full details of the production programme and copies of all SIGN guidelines are available from Juliet Harlen, SIGN secretariat, Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh EH2 1JQ or SIGN web page at <http://show.cee.hw.ac.uk./sign/home.htm>

In brief:

- Formal application and prioritisation procedure (e.g., enclosed British Society of Antimicrobial Chemotherapy jointly with Scottish Microbiology Association and British Infection Society).
- Multi professional development.
- Systematic reviews of literature.
- Evidence grading (levels 1a; 1b; 2; 3 and 4) linked explicitly to grades of recommendation (A, B, and C).
- SIGN Critical Appraisal of guidelines (see booklet)
- Local "translation", ownership and implementation
- Quality assurance, audit and feedback.
- 21 guidelines have been published (examples under separate cover from SIGN secretariat) e.g., 7: *Helicobacter*.
- 28 are in preparation (see schedule).

APPENDIX 2

Grampian Joint hospital-general practice Drug Formulary

- 1.1 Issued to all doctors (hospital and general practice) and to undergraduates
- 1.2 Compiled by BNF sections. The antibiotic section recommendations are based on local needs, organism sensitivities and agreement of key players (microbiologists; ID consultants; pharmacy; clinical pharmacology).
- 1.3 "Core drugs" for shared hospital and general practice use are agreed following discussions with "high users", specialists and practitioners; and local audit.
- 1.4 Formulary recommendations are *mandatory* in hospitals; monitoring of utilisation is and feed back undertaken by clinical (ward) pharmacists.
- 1.5 Formulary recommendations are *voluntary* in general practice. Yet coincidence (concurrence or compliance) of local general practitioner (c. 300) prescribing (SPA statistics) is 90–96 per cent for several key categories (beta blockers, calcium antagonists, lipid lowering drugs, ACE inhibitors. Health Board Medical Prescribing Advisor visits practices to discuss performance and setting of budgets.
- 1.6 Overview of drug utilisation patterns is undertaken by Grampian Medicines Committee with close involvement of Health Board.

2: Grampian Formulary selection procedures

Formal evidence based application is required for a drug to be included in the Formulary. Drugs are graded as

- (1a) essential for widespread availability;
- (1b) specialist indications only; prescribed by agreed specialists only; usage monitored closely;

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[Continued

- (2) "me too" drugs;
- (3) investigational and clinical trial use only; external funding required.

Examination of witnesses

DR HUGH MCGAVOCK, Director, Drug Utilisation Research Unit, Department of Therapeutics and Pharmacology, The Queen's University of Belfast; and PROFESSOR JAMES PETRIE, Head of Department of Medicine and Therapeutics, and DR JEREMY GRIMSHAW, Programme Director, Health Services Research Unit, University of Aberdeen, were called in and examined.

Chairman

633. Dr McGavock, Professor Petrie and Dr Grimshaw, thank you very much for coming along. For the record, if you could just introduce yourselves and make any opening statements that you may wish to make.

(Dr Grimshaw) I am Jeremy Grimshaw. I am Programme Director at the Health Services Research Unit in the University of Aberdeen. My particular area of research is how we implement research findings across all types of health care behaviours, so prescribing is one element of my global programme of work.

(Professor Petrie) I am Professor James Petrie. I am Head of the Department of Medicine and Therapeutics at the University of Aberdeen. I am a Clinical Pharmacologist. I am Head of the Scottish Royal Colleges Intercollegiate Guideline Network, which we call SIGN, and I also act as a consultant to the World Health Organization.

(Dr McGavock) I am Hugh McGavock, my Lord Chairman, from Belfast. I am the Director of the Drug Utilisation Research Unit at Queen's University, and our team researches the manner in which general practitioners and hospital doctors use medicines and, to a limited extent, how patients use medicines.

634. Thank you. Are there any opening comments you wish to make?

(Professor Petrie) I am not an expert on antibiotics but I am leading the SIGN national initiative in Scotland to try to get good evidence implemented into local practice. I am very pleased with the Scottish White Paper which is encouraging the commissioners of care to make evidence-based medicine happen at a local level. I believe that ownership of the evidence at a local level is what is important in implementing and securing the success of evidence-based policies.

(Dr Grimshaw) Likewise, I claim not to be an expert on prescribing antimicrobials, but I would reiterate that I see prescribing as a type of professional behaviour that can be influenced and we can consider evidence from a range of different interventions to influence different behaviours such as referral, test ordering, and diagnosis. The evidence I will present will be drawn from this wider literature but should be relevant to prescribing antimicrobials.

(Dr McGavock) My Lord Chairman, my unit has just finished a large-scale study on 21,400 general practitioner patient encounters of which 1,633 related

to diagnoses of upper respiratory infections. I have brought your Lordships a copy of the prepublication information on the ways in which general practitioners use antibiotics for the common cold, for sinusitis, for tonsillitis, for chest infections, for otitis media, which I think your Lordships will find very disturbing.

635. Perhaps we can start off a first question about COMPASS. You say in your documentation that "if fully utilized", it could save up to 15 per cent of prescribing costs. Subsequently, could you tell the Committee how you reached this figure and what measures need to be put into effect to produce this on a national scale?

(Dr McGavock) COMPASS is a quality based, evidence based computerised prescribing interrogation system. The acronym stands for Computerised On-line Monthly Prescribing Analysed for Science and Stewardship, which is actually, believe it or not, what it is! COMPASS compares each practice's prescribing every month in Northern Ireland against best practice and it then prints a clear report showing the ways in which the doctors did prescribe and recommends changes to improve the quality of their prescribing. The automatic question that all intelligent men and women ask then is "who decides upon the best practice?" Well, of course, we take advice from the best available specialists in each field, but to summarise the interrogation that COMPASS undertakes we have produced a thing which we call in Northern Ireland "The Five Commandments," which are easier to keep than ten! The five commandments are quite simple for both medical and non-medical people to understand. The first commandment is "avoid economic irrationality". If a drug can be purchased at one quarter, one tenth, one twentieth of the cost then you should prescribe as though you were paying for the drug yourself and treating your own family. The second commandment is "do not use drugs which are ineffectual". It may surprise your Lordships to know that many millions of pounds a year are spent in the United Kingdom by general practitioners prescribing drugs which are ineffectual. The third commandment is "avoid sledgehammers to crack nuts". I gave a talk on this to the German medical authorities and they said they had a similar metaphor which is, "You do not use a cannon to shoot a sparrow." Sad to say, it is the misapprehension of many of my medical colleagues that the most powerful drug is by nature the best drug, when in general practice a much less powerful drug is often the correct

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choice. So do not use sledgehammers except when you are cracking a block of concrete. The fourth commandment is "avoid new drugs until their claimed advantages have been proven". The uptake by general practitioners of new drugs I have shown in an update of my evidence to your Committee which shows about eight different therapeutic groups in which the take-off is the equivalent of the new Euro-fighter, in terms of sales figures. In none of those drugs is there any evidence of an equivalent increase in the amount of morbidity that they are used to treat nor of an increase in the severity of the conditions which they are used to treat. The last commandment is "avoid drugs with a poor risk benefit ratio". This refers mainly, but not exclusively, to the anti-rheumatic drugs, the non-steroidal anti-inflammatories. So those are the bases on which COMPASS is produced. It is powerful because it relates what the doctor actually did to what he or she might have done. As regards savings, the 15 per cent saving varies from month to month, sometimes it is 14 per cent, sometimes it is 16 per cent, but it means on about 15 per cent. This is calculated by taking the potential COMPASS savings of each practice in Northern Ireland and simply adding it up and it makes COMPASS a very powerful document because by adding up all the practices in an area board—it is the Family Health Service Authority in England—you then have the target which the Board Administrator should be aiming to save. By adding the targets for each area board to the region you then see what the regional administrators should be aiming to save. In six years' use we have never had COMPASS seriously challenged by any drug firm nor any doctor, certainly no challenge that we could not answer. I would emphasise that 15 per cent savings would have the effect of improving the quality of care, maybe not dramatically, but there would certainly be no reduction in quality of care. As regards costs, in Northern Ireland, including the cost of the part-time work producing COMPASS, it costs about £2 per copy. My colleagues in the Department of Health in Leeds in the National Health Service Executive are aware of COMPASS as is my medical colleague the Medical Director of the Prescription Pricing Authority in Newcastle-Upon-Tyne.

Lord Dixon-Smith

636. You say that you research what is going on in general practice and you compile the results for each practice and then obviously you consolidate those. Presumably each practice's results are then fed back to that practice.

(Dr McGavock) Yes.

637. Do you find the general practitioners then absorb the lessons from your compilation and are they changing their prescription practice to produce the results that you predict ought to be achievable?

(Dr McGavock) That is clearly a very important question. I have been disappointed at the results of COMPASS simply because, for reasons not clear to me, it has never been fully implemented in Northern Ireland. Where it has been fully implemented, as for

example by the fundholders, it has been very popular. Some fundholding practices wish to have a copy every month which I believe to be excessive as once a quarter would be plenty. I think the figures are somewhere in the order of £20 million saved in Northern Ireland by fundholding practices in the last three years. The only evidence I can give for non-fundholding practices is that this time last year the 60 non-fundholding practices in Belfast made a pact with the then Minister of Health, Mr Malcolm Moss, that if he would put £600,000 into the kitty to restore elective surgery for non-fundholding patients in our big teaching hospitals, they would undertake to save that amount in January, February and March 1997. I went round lecturing and the area medical advisers visited them and in those three months they saved £1.2 million. If you scale that up to one year that clearly comes to £4.8 million and if you scale that up to Northern Ireland you end up with about £28 million a year to get better practice.

Chairman

638. What is it going to take to get this more on a national scale, because your figures are very impressive on savings?

(Dr McGavock) I believe, my Lord Chairman, that doctors require some incentive. As I think my evidence may have indicated to you, prescribing is a learned behaviour and like all behaviours is extremely difficult to change. It is stressful to change for the doctor, the receptionist, the patient, the pharmacist. I truly believe it is not unreasonable to offer some form of incentive. The fundholding scheme did that and the non-fundholding doctors in Belfast also did that. Their only incentive was *pro bono publico*. I advised the Department of Health in Dublin some years ago and they devised a 50:50 split; 50 per cent of savings went back to the practice for practice affairs, not into the doctors' pockets, and 50 per cent went back to the Department of Health. Clearly, as with fundholding, savings are made for the first two/three years after which it is impossible to save more and costs will then begin to rise again. I do believe that incentive is essential. General practitioners—I speak as a GP of 12 years' duration in a previous life—work extremely hard, in my opinion offer an extremely good, sympathetic, personal service. In my work with general practitioners my opinion of them over the last 17 years has actually steadily risen and it is not unreasonable in a materialistic world to offer them some decent incentive for this exercise.

Baroness Masham of Ilton

639. Is it not better sometimes to crack an infection on the head quickly rather than going on with a softer drug that will take longer?

(Dr McGavock) It is not the case that using the widest spectrum antibiotic will necessarily be the best treatment. For example, if I had a patient with acute broncho-pneumonia I might well, if I believed the drug advertisements, give them a drug called ciprofloxacin, which is a very powerful antibiotic, or I might have

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given them benzyl penicillin which was produced in the 1940s. The fact is were I to give them the expensive broad spectrum sledgehammer, in three days' time it is quite probable that I would have to give them the intravenous benzyl penicillin to kill the bacteria which the ciprofloxacin had not killed, the pneumococcus. There are many many examples where the weaker drug is the correct treatment and will produce better immediate and long-term results.

Lord Rea

640. Penicillin by injection is not a weaker drug, it is the strongest drug for the particular infection you are talking about.

(*Dr McGavock*) That is the point I was trying to make.

Chairman

641. In your evidence you say that waiting two to three days before prescribing "often results in more complete resolution and seldom harms the patient." What are the situations where postponing therapy would pose unacceptable risks?

(*Dr McGavock*) Clearly, there are such cases and in general I think evidence of systemic infection would lead me as a general practitioner to prescribe, presumably a raised temperature, an ill patient and a variety of other signs. For example, in the case of meningitis, meningism. In the case of abdominal infection, signs of pain. In the case of renal tract infection, pus in the urine and so forth. My estimate of the frequency of that occurrence in general practice would be one case a fortnight, one case a month maybe. The vast majority of illness that we see in general practice is self-limiting and if nothing were done, would get better.

642. Some of us were over in the United States recently and this is an issue which they struggle with too. There they have the legal aspects which are particularly important. It seems to be less important in this country. Could you comment on that? The practitioners in the US would say they have to give drugs because of litigation, otherwise if anything happens they will have a \$1 million suit on their hands.

(*Dr McGavock*) Presumably their legal advisers are poorly advised microbiologically. As a doctor I would be much more concerned about litigation over iatrogenic disease, disease caused by the drugs I had prescribed unnecessarily. As your Lordships will see in this doctoral thesis which has not yet been published in medical literature, the amount of antibiotics given for respiratory infection, upper respiratory and lower respiratory infection unnecessarily (70 per cent of it is viral in origin and will not be affected by antibiotics) means all of those patients are receiving nothing but risk when they are given an antibiotic, no benefit whatever, only risk and I would be much more

concerned to stand up in court to justify my actions in prescribing unnecessarily.

Lord Porter of Luddenham

643. That is a view which I am sure all medically qualified people would go along with, but unfortunately there is nothing the lawyers can gain from that, is there? You cannot bring a case. There is no litigation which is going to help you not to prescribe.

(*Dr McGavock*) No.

644. So the doctor is playing safe here.

(*Dr McGavock*) My experience over 17 years working with the Northern Ireland Civil Service as the liaison person to doctors, especially on prescribing, has been that if anything motivates doctors it is the desire to be as good a doctor as they can hope to be. With 99 per cent of doctors I meet, this is the most powerful motivator. That is what one must aim for, to prick the very delicate conscience of most physicians.

Lord Perry of Walton

645. You say on the second page of your evidence, "In the case of upper respiratory tract infections, by far the commonest infectious diagnosis in general practice, most doctors are aware that 70 per cent of cases are viral in origin and will not respond ..." and then you go on to say 80 per cent of the patients were given an antimicrobial. I want to get on to the point of drug resistance rather than saving money. We came across comparable figures in the United States where they said the commonest condition that they encountered in general practice was otitis media. Otitis media is very similar in that, again, well over 50 per cent are probably viral and 40 per cent are probably short-lived and do not require anything for a couple of days, and only ten per cent will require an antibiotic. What antibiotics do your GPs use for upper respiratory tract infections and what is the rate of resistant strains that are found in those that are looked at in the lab? I know that only a small proportion will be. What do you think the hazard of creating more resistant strains is by the use of antibiotics in this way?

(*Dr McGavock*) I actually have in the evidence that I brought with me, which I will leave with you, a list of antimicrobials used in all of the various upper respiratory conditions and these vary both in frequency of use and in the actual antimicrobial. For example, for the common cold the antimicrobials used were phenoxymethyl penicillin, a broad spectrum penicillin, usually amoxycillin, macrolides, that is drugs like erythromycin, cephalosporins, the trimethoprim drugs and the tetracyclines, all of those for the common cold and about half of them prescribed without a consultation.

646. But what is the rate of drug resistance to these particular antibiotics?

(*Dr McGavock*) There are resistant organisms to all of these and multi-resistance in some cases.

647. In figure 2 of your paper you show the number of defined daily doses per 1,000 patients in the

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case of penicillin which is 160 per 1,000. That is a very high proportion of patients getting treatment.

(*Dr McGavock*) Especially since they are being given for the common cold and for other respiratory infections which may or may not be viral. It is a situation that really must be changed if we wish to preserve the antimicrobial era. It simply cannot go on. Well, it can go on, of course and it may well go on, but if it does our grandchildren will curse us for wasting this limited human resource.

648. Professor Petrie, you said that the Grampian Drug Formulary recommendations are voluntary in general practice. Can you tell us what the level of compliance is in respect of the common antibiotics? Can you tell us anything about the resistance rates there?

(*Professor Petrie*) I would ideally like to preface how we develop the Formulary, but I will give you the straight answer. For the groups of drugs that have been discussed by the local specialists with the teams of local general practitioners we have 100 volunteer general practitioners. A sub-group is working with the microbiologists, looking at local resistance patterns and patterns of drug use. We have got an agreement on a core of drugs. The coincidence for, say, three calcium antagonists is up at 96 per cent; for two beta blockers it is in the high nineties; antibiotics is about 92 per cent. Coincidence is way up because we have agreed locally on what we should do. As I said in my evidence, the hospital formulary is mandatory so there is no choice and the compliance with the formulary is monitored by ward pharmacists who go round all the time. In general practice the formulary is voluntary. In the light of experience we have just revised the remit of our local Drug and Therapeutics Committee. In future the Committee will receive drug utilisation data and target priority areas to go out to monitor coincidence. We believe that ownership of policies makes an awful lot of difference in terms of compliance. This is a partnership between the local microbiologists, the local infection specialists and the local GPs. It is quite a remarkable co-operation.

649. How far is the advice based on your knowledge about the resistant strains?

(*Professor Petrie*) It is not based on my knowledge because I act as a quality assurance person and I chair the Therapeutics Committee, but the Committee insists that the local microbiologists are involved. A major point your Lordships may be interested in is that the sensitivity discs used to be issued to the local laboratories by the drug companies with their drugs specified. Now the microbiologists only report to the local general practitioners those drugs on the locally agreed Formulary. So that has had a huge impact. If you get the sensitivities from the drug companies the practitioners will get the company drugs printing out. If it is your locally agreed drugs that are reported on you then help to get the right compliance. The list of drugs is continuously updated with local microbiological input.

Lord Dixon-Smith

650. Can we go back to Dr McGavock again. You say in your paper, "Every GP in the United Kingdom has open access to bacteriological laboratories which can supply scientific evidence of bacterial infection together with the appropriate antibiotic, usually within three days." There is another thought about taking horses to water and whether or not they will drink. Realistically, in what situations should a GP seek laboratory analysis? Presumably, since these laboratories are already busy, this would mean an expansion of the laboratory service. Have you tried to make any assessment of what this would cost and who should pay that cost?

(*Dr McGavock*) This is really a question for a microbiologist, my Lord. However, I have problems with the word "realistic". When mankind attempts to manipulate the living world, and particularly the world of micro-organisms, he declares war on a very powerful opponent and in war you either survive or you die. If you wish to survive in this particular war, if you do not wish people to die of carbuncles, pneumonia, meningitis, finger prick septicemia in the prime of life, as happened when I was a boy, then whatever you are required to spend you must spend. I would be loath to say that general practitioners should send microbiological bacteriological specimens in every case they see because, as I have already said, most of the illness they see is self-limiting and if nothing is done will get better, including many of the infections. I would really want to leave it to a microbiologist to answer that question. However, if it takes a four-fold increase in the availability of bacteriology then so be it. This resource is well worth preserving. For a pharmacist to dispense any of the modern powerful broad spectrum antimicrobials the general practitioner ought to have to supply bacteriological evidence that that drug was necessary in most cases. The other thing that would help greatly, which would not involve any statutory control but would undoubtedly be unpopular with the drug industry, is that all hospital-only antibiotics, including many of the antibiotics that are used in general practice today, should be available by injection only because if they are available by injection only, general practitioners will not use them.

651. Has anybody got a guess at what the cost of the bacteriological laboratories is as a proportion of total Health Service costs? Are we talking about one per cent, five per cent or a fraction of a percentage point?

(*Dr McGavock*) The cost of hospital work?

652. The cost of the bacteriological laboratories as a proportion of Health Service costs.

(*Professor Petrie*) I cannot answer particularly with antibiotics but I can with some of the haematological drugs where the actual add-on costs, which are non-drug costs, may be five or six times more than the actual costs of the drug.

653. It is the actual laboratory costs I am worried about.

(*Professor Petrie*) The staff costs, the add-on costs and the process costs dwarf the drug costs and in my

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view the drugs are the least part of the process of care. I do not agree that we can swab everybody. This would paralyse the system. We cannot do urinary tract tests on everybody. Practitioners need, preferably, nationally evidence-based statements from key people to say "You do this" or "You do not do that" and then locally practitioners should review and then "own" the advice. Local education initiatives and feedback make the policies work. We do not want to be reinventing wheels or making statements about throat swabbing everybody or getting urine tests for everybody. It is not realistic and it would cost a fortune and paralyse the system.

Chairman

654. Surely the most practical thing in terms of what we are talking about, of taking specimens, is a throat swab.

(*Professor Petrie*) I am not an expert, but I have worked with Professor John Howie from Edinburgh who Lord Perry knows well. He did a lovely study some years ago. Unfortunately, because of modern retrieval methods old studies seem to get less weight than new studies. He took pictures of sore throats and underneath them he put a legend saying, "This is a Lord's son" and "This is a coal miner's son". The prescribing depended on the social and other factors rather than on the appearance of the throat. I think that is a very powerful study. We went through the argument about throat swabs 20 years ago and found that theoretically you should do them but in practice doctors do not do them and it is really an unnecessary thing to do. It is difficult to persuade doctors because of the social pressures that you did not give the Lord's son the antibiotics. This is a real problem, so doctors opt out and prescribe. May I just add another thing from earlier? I was shocked to find that our local GP co-operative that works at night—we call it G-Docs—gets free starter packs from drug companies. The free starter pack is co-amoxiclav. That to me is bizarre in that this is, going back to Baroness Masham's point, a sledgehammer to crack a nut. This company practice provides free drugs, loss leaders and affects the work on resistance that you are doing and it worries me considerably.

Lord Winston

655. As a practising clinician I see a huge proportion of bacteriological samples come back with non-specific, non-identifying or useless information. What I would like to get a feel of is just how frequently that would happen with specimens which are sent by general practitioners, i.e. effectively a bacteriological sample which has been plated up.

(*Professor Petrie*) I am not an expert in this field. We know—and Professor Wise and Professor Lambert know well—that urinary infection in general practice will be an E.coli in 90+ per cent of cases. Trimethoprim alone will secure a cure in 95 per cent. The new drugs are just making one or two percentages differences but costing a lot more. So it is really

unnecessary to do the tests unless the infection persists.

Lord Porter of Luddenham

656. Dr McGavock, you suggested that perhaps a four-fold increase, if that were necessary, should be taken up in bacteriological laboratories and then we would have to cope with the extra costs. Would there necessarily be an extra cost? Could not this work the other way round? If one had more bacteriological testing many of those would be negative, they would give the answer that further prescribing of antibiotics is not necessary and this would save money. Do you feel that this would be a balancing act?

(*Dr McGavock*) First of all, my Lord, I would agree entirely with what Professor Petrie said, which is similar to what I said before, that the vast majority of conditions in general practice are self-limiting, will get better without medical treatment and do not require bacteriology. What worries me greatly is the use of so many important modern antimicrobials like ciprofloxacin and norfloxacin and ofloxacin and clarithromycin, azithromycin without bacteriological evidence. If a doctor feels justified in giving any of those drugs in my opinion he should have bacteriology in front of him.

657. This is a cost that has to be borne? Would there be no payback the other way because of better knowledge and the information that such drugs are not necessarily effective?

(*Dr McGavock*) I think what you ask brings up a terribly important point which is, which antimicrobial should a general practitioner use? The answer has been there for the last 30 years because for the last 30 years the British National Formulary has had Table one—and I do not know if there is another table in the Formulary proper—and every six months Table one is updated and Table one gives a list of the correct presumptive antimicrobial treatments for all of the main conditions presenting at general practice and hardly any of those drugs I have mentioned appear in Table one. If general practitioners can simply be persuaded to stick to Table one in the British National Formulary then I believe that of itself would achieve a great deal of what your Lordships wish to see done.

(*Professor Petrie*) My motto for our Therapeutics Committee is that patients should get the drugs they need irrespective of cost. If a citizen needs a drug, we—the doctors and the patients—should be advocates for that citizen, but we waste so much money on unnecessary drugs that we can ill afford expensive drugs. We need to educate the patients in terms of what their expectations should be. The other thing we are going to talk about later, the SIGN intercollegiate guidelines network, is where we are involving patient associations to help us to put across the key messages in regard to sore throats and urinary infections. The recommendations must be based on solid evidence of most respected authorities so that people believe them. There are patient demands which are fed by commercial interests which, of course, have to make money for their shareholders. Another starter pack

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which is given to the GP: co-operatives is clarithromycin. Again, it is very unfortunate that these co-operatives should get free drugs starting with clarithromycin instead of erythromycin in primary care where there is not the resistance that happens in hospitals.

Baroness Platt of Writtle

658. Dr McGavock, you strongly favour that bacteriological tests before prescribing be made mandatory except in the case of "critical infection". Is that a practical idea and what other statutory methods might be possible?

(*Dr McGavock*) It is a very searching and difficult question. I would simply repeat what I said which is, first of all, there should be no oral form of any important new broad spectrum antimicrobial. They should be by injection only, therefore restricting them almost entirely to hospital use. The second thing is that I believe that general practitioner antimicrobial prescribing should be restricted to the recommendations of Table one of the British National Formulary which represents best practice updated every six months. I do believe that you need a national organization similar to our Drug Utilisation Research Unit to monitor the effects of your interventions and the outcomes, if any, both in terms of quality and in terms of cost. It may be that penalties are required for doctors who are unwilling to abide by the guidelines, that is not for me to say and perhaps rewards should be offered to those who do. The French do this right through their prescribing. Those French general practitioners who abide by the guidelines for any therapeutic area receive something like five per cent extra salary. Those who fail to abide by them get nothing. Those who persistently ignore them are fined. This seems to me quite reasonable in the modern world.

Baroness Masham of Ilton

659. Would it not be better if the whole system was speeded up? I live in a rural area and it takes an awful long time to get the results. It takes an awful long time for people to see their doctors. I live in a farming community, the farmers are under stress, they want to get out and look after their animals and the whole thing takes such a long time. It would be good if one could get good speedy tests, the result, the right antibiotic, get the patients better, but it is not practical to give them injections in hospital because most of the hospitals have closed down.

(*Dr McGavock*) That is an important point. The fact is that for perhaps 95 per cent of infectious conditions in general practice it is best to do nothing except perhaps take a cough medicine for two or three days as that will actually benefit the patient because in that time the patient's immune system will be mounting its own defence. So the two or three days' delay before an antimicrobial is given should be beneficial. Studies in America and in Holland have shown that with an ear infection in children, to withhold an antibiotic for 48 to 72 hours and then give

it, if necessary, reduces the recurrence rate to one fifth of the recurrence rate when an antimicrobial is given immediately.

(*Professor Petrie*) In my work with the World Health Organization I have observed that some governments have no statutory controls for antibiotics. It is important that antibiotics do not go for sale "over the counter", that is one of the issues. With European legislation some other groups of drugs are now becoming available over the counter where there is no risk to the public health. The Committee on Safety of Medicines, as you know, in its statutory function looks at the safety of drugs. In the new White Paper the prospect of a National Drugs Committee has been signalled which may be looking more at reducing the inequalities in the local availability of drugs. I welcome the idea that you look more now towards the need for drugs, but I think statutory legislation on that would be most unfortunate because I think it has to be professionally led and I suspect that regulators would have difficulty in deciding on need. It is really up to society to decide whether we need some of these new expensive drugs, but if we do need them I think we need local systems of using the drugs appropriately with good monitoring of prescribing and care. So if a new expensive drug becomes available we should know to whom it is going, is it appropriate and monitor it. Through such systems we can monitor use and better afford the expensive drugs for those that need it. But the professions must argue against wanton salesmanship of the very latest drugs resulting in their being prescribed to the people who least need them. If Professor Wise and Professor Lambert, backed up by evidence, were to say to the citizens, "If you have a sore throat you do not need X" the citizen would accept that. The citizen would be reassured by an authoritative view and not by GOBSAT,— Good Old Boys (or girls) Sat At Table—opinion, or "I think, therefore it is".

Lord Jenkin of Roding

660. The footnote at the bottom of the third page of Dr McGavock's evidence says: "Since DHSS (NI) has withdrawn financial support for DURU from 28th February 1998, it is unlikely that these factors will be researched further." Dr McGavock, you make yourself sound a little bit like a voice crying in the wilderness. You are asking for statutory controls on medical practitioners' freedom to treat their patients, and such controls would, without any doubt, severely harm the profitability of the drug companies. Are you not tilting at two very big windmills and is this the reason why your grant has been withdrawn?

(*Dr McGavock*) No, it is a result of Government policy that there should be no independent core-funded research units working for the DHSS. The same thing happened to my colleagues in the Prescribing Unit in Leeds and to other units as well. It was a national policy. I believe my colleagues in the Northern Ireland Civil Service are satisfied with our work, as they have good reason to be. Might I take up what Professor Petrie has said also? Yes, of course as a democrat I would like to see everything happen by agreement, but

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our work over the last seven years has shown that no matter what aspect of general practice you investigate you end up with a frequency distribution curve of activity, whether it is the number of consultations per month per doctor or the number of antibiotics given per 1,000 patients which I brought in the new evidence. As I said earlier, we are engaged in a war for the survival of the antimicrobial era. That is not an overstatement. My microbiological colleagues in the Royal Victoria Hospital in Belfast and other hospitals assure me that that is not an overstatement. They are sometimes left with one antimicrobial choice for a life-threatening illness. In such cases the liberty that my GP colleagues prize so much is not liberty, it is licence. If we allow the frequency distribution simply to run, with some doctors accepting the guidelines perfectly, the majority moderately well and some doctors on the far side of the curve hardly paying any attention to them, we are simply speeding up what is already happening, the end of the antimicrobial era. No one has mentioned the fact that 40 per cent of our problem is the agricultural industry.

661. We have had a lot of evidence on that.

(*Dr McGavock*) Indeed. So it is not that I am not a democrat, it is just in war democracy takes a back seat, and this is a war. I do not wish to see my grandchildren dying of diseases which today would be cured in 48 hours.

662. Can I say it is very reassuring it is not because of the nature of your work you have lost your grant, but on the other hand I think you can hardly expect the pharmaceutical industry to jump in and fill the gap, can you? Who is going to fund this work?

(*Dr McGavock*) This is the sad thing. A unit such as ours is only going to be funded by the authorities, by Government, by local authorities. It is not going to get funding from the drug industry, simply because so much of our work indicates the over-use of unnecessarily powerful drugs.

Baroness McFarlane of Llandaff

663. Professor Petrie, you have already mentioned the Scottish Royal Colleges Intercollegiate Guidelines Network and we would like you to describe that to us. The only infectious disease listed in your Guideline Development Programme is *helicobacter pylori* in the context of dyspeptic disease. Do you plan to produce guidelines for other infectious diseases in due course? What is the level of penetration of the SIGN Guidelines and what is being done to monitor compliance?

(*Professor Petrie*) The Intercollegiate group is the Royal Colleges in Scotland plus all the Faculties of the English Royal Colleges, so it is a big group. I am pleased to say a lot of the English Colleges are now beginning to work on an intercollegiate basis on our model. We have also included nurses, representing the Royal College of Nursing, the Chief Pharmacist of Scotland is involved, the dental services are involved, professions allied to medicine are involved and patients are involved, and the Chairman of the Scottish Local Health Council is involved. So it is more than

an intercollegiate guideline group, it has a wide ownership. The Scottish Health Service managers are involved as well. SIGN is professionally-led as opposed to being statutorily-led. It happened by accident, it was not a grand plan. The College of Physicians in Edinburgh with the Royal College of General Practitioners thought it would be nice to stop complaining about things and to give some leadership, which is of course what we have done. We started off not really knowing where we were going and our initial topics were based on enthusiasts and we would not choose some of them again. Now, thanks to Professor Robert Kendell, who was the Chief Medical Officer, we are beginning to focus on priority topics for the health services where there is evidence that was not being put into practice; where we knew there were widespread variations in practice, perhaps at a high cost; or low costs and high volumes. So we now have a very careful application procedure for inclusion in the programme. It happens that the number seven SIGN guideline was *Helicobacter* and that has had a huge impact, for example, in Tayside where 12 per cent of the drug budget was to do with *Helicobacter*. We are talking here of £10 million. That has gone right down through the implementation of triple drug therapy in appropriate patients. SIGN has a guideline which is now about to come out on tonsillectomy, which again will answer some of your questions. The SIGN guidelines are based on multi-professional development, so you have a table with lots of key players who implement later. So SIGN is multi-professional, it is geographically representative, so we get the best people from around the place, and it has all the players. The guidelines are based on very sophisticated literature reviews. These are not Cochrane Reviews. In my opinion, it is nice to have a Cochrane Review but it requires so much work that you are almost paralysed by analysis. Practitioners need pragmatic solutions fairly soon. It is for other groups to go out into the wider literature and the other nations of the world and into the so-called "grey literature" where you write to the companies and say, "Do you have any negative studies we should know about?" Let us get the principal facts out as soon as feasible and start implementing them. So SIGN is multi-professional, geographic and evidence-based. So *Helicobacter* was good on that. Tonsillectomy we are doing. We have also learned not to tackle too much at one time—"salami slice", as I call it. SIGN will consider otitis media but not until that group of specialists get experience of developing the SIGN methodology. There is a SIGN guideline published on acute asthma which has some antibiotic bits in it. SIGN has "salami-sliced" asthma, and there is a guideline on asthma in hospitals, asthma in schools, asthma in general practice, asthma in A & E. We also have got a recent submission to SIGN, which we have approved, from the Society of Infection on proposed guidelines to optimise the recognition of sepsis and guidelines to optimise the route and duration of antibiotics in surgical prophylaxis. SIGN looked at this remit and thought, "That is too big, the guidelines should focus more on that which is important in terms of antibiotic resistance". So, the answer to your

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question is yes, SIGN has some more guidelines in the pipeline but to date antibiotics were not a priority, because as you know the nation's priorities, in Scotland at least, are cancer, cardio-vascular disease and stroke and mental health. But SIGN now recognises that antibiotics are important and so SIGN are beginning to consider this problem.

Briefly, the evidence in SIGN guidelines is graded by levels of evidence, so level 1a is the best, where there is what we call meta-analysis, lots of trials showing definite things are happening. A 1a or 1b results in a Grade A recommendation. We believe, and the Health Service in Scotland believe, if we could implement these Grade A recommendations through the health authorities, trusts and primary care, with the support of the patients, we would improve prescribing practice and care of patients with stroke, diabetes, and asthma. We have now published 21 guidelines—we just published a guidelines on epilepsy yesterday—and we have 48 on the stocks at the moment. So we have a rolling programme of developing evidence-based guidelines based on levels of evidence and grades of recommendation. I should say the Royal College of General Practitioners in Scotland and in fact in the United Kingdom have been very helpful. In each area they have lead GP groups to promote the SIGN guidelines and make them happen. The patient associations have been super in the sense of preparing notes for patients, and again the *Scotsman* and various other newspapers are helping us in this. I do not want to go on about it but the SIGN initiative is based on national evidence-based guidelines which we keep fairly thin and then we need the local ownership of the recommendations, through discussion. Those are really the pivotal points. I think that the SIGN methodology, which is a little bit like the formulary methodology, where you have a nationally-agreed policy and then implement it locally partly through education, is important. Each SIGN guideline is subjected to national meetings and for the breast cancer guideline, which is again on the stocks, we had 250 people who came to the Royal Colleges to listen, for the stroke guidelines we had 400. So there are wide discussions going on which influence behaviour in a major way. Also by audit of what people are doing, you can get the “outliers” and bring them into the middle group of prescribers voluntarily. If you start going out with guns and statutory controls, people hide, and you get a lot of resistance. So we have the support in Scotland of the professions and of the BMA. At the outset I was advised to be wary of taking the BMA on board, but SIGN did, because we have to be realistic to implement evidence-based practice, and need the goodwill of the patients and the goodwill of the doctors and other professions, because often it is the nurses or pharmacists who will make things happen, not the doctors.

664. So really what kind of hard evidence is there of compliance? Because in educational terms, giving people information is not enough, is it? How do you change behaviour?

(Professor Petrie) Dr Grimshaw is a world expert on this but there is clear evidence that simply sending

out a guideline is a waste of time, it just goes into a bucket, we know that; that is a fact. You need the local translation and in Scotland Clinical Effectiveness groups have been set up in each health board to take a lead in this issue and to co-ordinate with what I earlier called the process of care, not just the drugs but the process of the delivery of care. This goes right down in hospitals to the directorate systems. The Scottish Council for Post-Graduate Dental and Medical Education also uses this, as do the Colleges, when they inspect trainee general practices, “Have you got the guideline in place, will your post be accredited, are you using the SIGN guidelines?” So we have that sort of control but also there are a host of studies going on in Scotland around these guidelines, because Government in Scotland has said, “To audit, audit around the SIGN guidelines.” So we now know with various guidelines—I will not take you through them—there has been a revolution in what is happening. In, say, diabetes, eyes are getting looked at, feet are getting looked at. Patients are getting educated on discharge who have asthma, which prevents re-admission. The same with fractured hips, strokes. It has given a focus for change in the Health Service which before was affected by what I call the “flat earth” mentality, where everybody said, “It is impossible. We cannot do anything.” This has given leadership and we are all working together to achieve that.

Chairman

665. Associated with doctors' behaviour of course is patient expectation.

(Professor Petrie) Yes.

666. Have you any comments on that?

(Professor Petrie) We have a very effective patient representative called Patricia Dawson in Scotland who leads the Scottish Local Health Councils, and she has been educating them about the SIGN process. There is a difficulty in telling patients too much too soon, if you like, before the profession is ready, and so we are trying to warn the doctors of the key messages in these guidelines and now, with the NHS Net, our proposals are to put the key messages out on the InterNet, which doctors use for safety of medicines type alerts, to say that in six weeks' or two months' time, key messages will be coming out. We have press launches which have been prepared with the patients and we co-ordinate that. Because there is a danger of antagonising the profession if you publish evidence which they have not heard about, or they hear about it in the news. So we are looking at that. We had a problem with a SIGN Obesity guideline where there were problems about the withdrawal of a very important drug, and we have to manage the process of how doctors are informed alongside patients.

Lord Perry of Walton

667. You quote the priorities as having been cancer and cardio-vascular disease. Is it not likely that there is a far bigger threat to public health from drug

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resistance than any of these things and yet you have not actually started on this?

(*Professor Petrie*) As I said, we started out by accident along the SIGN path, and you have just reminded me that we have just accepted chlamydia as another problem. The funding for SIGN, which might interest you, which we get from the Scottish Office and the Royal Colleges is £130,000, and I think it is pretty good value for money to get all this output compared with the millions we are throwing away on drugs. The rest of our budget is spent on printing. Although I said the national priorities were these three things, the Scottish Office has been very far-sighted and said that if the professions wish to come forward with other topics, they will be happy to consider them for funding. So we are able to bring forward whatever we like as professionals, and that is why tonsillectomy, chlamydia and others have come forward. If your Lordships were to come forward and say that you think this antibiotic resistance important, it could well be that more things would come forward, but I am very encouraged by this application from these micro-biologists which set us down that path.

Chairman

668. One point about SIGN, you say in your document that it is pharmacists, nursing and professions allied to medicine, et cetera, and we have heard earlier today from Dr McGavock of the problem on the animal side. Is there any possibility of bringing animal medicines and the use of antibiotics into your SIGN programme, or is that not part of your plans?

(*Professor Petrie*) SIGN is a methodology organization, almost a quality assurance organization. We try and quality-assure the process of development so we would ask an individual to take a group forward. We would be careful who the chairman was, who the members were, but SIGN does not believe it can do guidelines for everything. That is why I am so pleased that different colleges—for example the colleges in London—are taking the lead in certain areas to this sort of methodology. I would like Dr Grimshaw to explain how there is a European dimension to this as well, where Europeans are taking this on. So as long as you go through these sort of criteria for appraisal which I have given to the Committee—these are 53 points we would like groups who are preparing guidelines to follow—I do not see why any group such as veterinarian medicine could not set up a similar process but I think it would be too much for SIGN itself to do. It may be SIGN in due course will expire, but I would hope the methodology will live on.

(*Dr Grimshaw*) I will restrict my comments to issues on synthesis of knowledge, which is what SIGN and other guideline initiatives are trying to do. When we are trying to change behaviour, I see a two-step process. The first is to try to provide a clear synthesis of the available evidence. It is impossible for any individual practitioner in health care to keep up to date. I think the last estimate was that there were about 20,000 journals published each year and a general practitioner would probably have some interest in the majority of those, even in specialist areas it is very

difficult to keep up to date. So when we are talking about issues of antimicrobial resistance and treatment of infections, it is very hard for health care professionals by themselves to keep up to date, and this is why we need to move towards secondary synthesis of information. There are two broad types. The first is systematic reviews of the type undertaken by the Cochrane Collaboration, which use explicit methods to try and reduce bias in the review process and over time will produce gold standard information which will feed into guidelines. Guidelines often consider disease management and antibiotics use may be part of that. Over the last five years there has been an international revolution in how we develop guidelines. If you look back maybe 10 years, we would have used what Professor Petrie referred to as the GOBSAT method—Good Old Boys Sat Around a Table. Starting in America but now internationally followed, people recognise the need to use explicit methods—multidisciplinary groups, systematic reviews, evidence-linkage—as a way to provide the best information for health care professionals. That is the approach SIGN has taken. There are similar approaches in England and Wales, and particularly the commissioning of guidelines from Royal Colleges over the last 12 to 18 months have promoted the use of these explicit methods. In Scotland there is an issue about how we integrate into these initiatives so we do not duplicate effort. Likewise, across Europe, there is a European funded project to develop a European critical appraisal group of guidelines, involving partners in eleven countries and Canada. I think this will start to move towards greater homogeneity in how guidelines are being produced and greater efficiency in the fact we will be able to use the literature reviews produced in Spain as the evidence base for guidelines to be developed here. I think across all areas of health care there is this movement which should provide a focus for the type of recommendations that you may want to make around antimicrobial resistance and interventions which take that forward. That is all I want to say about the synthesis of knowledge, although we will come back in later questions about how we help professionals to use that knowledge.

(*Dr McGavock*) I would like to simply complement my two colleagues' comments on two points. First of all, to remind your Lordships of the great importance to the medical community and to health care, to patients, of the person who may not actually do research on medicines or on diseases but who is capable to distilling the essence of 100, 200 research articles into a form that is digestible for the individual practitioner whether in hospital or general practice. Only people like Professor Petrie and Dr Grimshaw and myself who have actually been involved in this exercise know how difficult it is. The way has been shown clearly by my friend and colleague, Dr Andrew Herxheimer, in his work with the *Drug and Therapeutics Bulletin* over 30 years, and now his work with the Cochrane Collaboration, the work of the *Adverse Drug Reaction Bulletin* by Professor Davies, and the excellent work of the Medicines Resource Centre in Liverpool with the *MeReC Bulletin*. I believe that this group of scientific

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workers is going to become more and more important as medicines become more and more complex. The second point is that I do believe it is worth re-emphasising that doctors applying such guidelines as the SIGN ought to be rewarded for doing so, not in terms of a large amount of money but certainly in terms of the French pattern, and perhaps the fact that those who do not abide by the guidelines get nothing is punishment enough.

(Professor Petrie) I think if you want to implement changes through guidelines, the implementation of the guidelines is the challenge. Preparing the evidence is relatively easy in a funny way. We need to find a tool for implementation. What that tool is we are all struggling with. Quality assurance is probably the word but it is how to deliver that, and whether it is by the commissioner of the service saying, "If you are providing diabetic services you must look at the eyes every year, the feet every year, the kidneys every year"; if you are providing an infection service what guidelines are you using? What consultation processes have you in place locally? What structures have you in place locally? What data do you collect locally in order that there can be a local review of what is happening? I think a national review of drugs has much less impact on local implementation of formularies than a local review of drugs where you can rearrange your problems locally without declaring them publicly. There is an increasing move to ask the provider of care to provide the data on what he is doing, to demonstrate he is getting value for money. So I would not pay him more, I would say, "Why should we pay you unless you are providing a quality service", because a lot of money goes out and we do not know what we are getting for that money. So by defining standards which are voluntary and by people signing up to these standards, I believe you get a better quality of care. The second point which I have just mentioned is that these SIGN guidelines are now on the InterNet, and I think we have had, without publicising them at all, over 50,000 hits which represents over 40 per cent of the Scottish Health Service's activity on the Net. We know the Malaysians, for example, have just picked the diabetes eye guideline and said, "Care of Diabetic Patients in Malaysia" and just taken it on. There is a huge international interest in this and through the Net patients can get access to that. Patients are the agents for change and if patients can get involved in a constructive way it would be terribly helpful to all of us who want to improve prescribing in general.

Baroness Masham of Ilton

669. Please tell us about the World Health Organisation's Essential Drug Programme. What impact can it have on the abuse of antibiotics in countries with less developed health services than ours? I know working with HIV we have been told that venereal diseases in Africa are really rife.

(Professor Petrie) I do not want to spend too long on the WHO Essential Drugs Programme, but I have been involved with this for ten or fifteen years and all I have been saying about local formularies and SIGN

relates to that programme. When many of us first heard about the Essential Drugs Programme, we were pretty opposed to it because it looked as though some people had said, "These are the 29 drugs you, poor nation, will use", or perhaps 59, 79, there were different levels, and people said, "Who are these chaps in WHO in Geneva to tell them what to do when they have never been there?" I call it an Aunt Sally list, it is a list to argue with, to get cross with and change and own locally. But through such discussion you educate the multi-professional teams in each nation, if you like, and then in each locality. So this principle of having this "Aunt Sally" list means that whatever you are talking about, you get the local ownership of that. I believe for antibiotics that you need that "Aunt Sally" challenge from national guidelines for local revision according to sensitivities and local discussions according to the prejudices of the local people. The principles of the WHO Essential Drugs list are important and I have advised the refugee camps in Palestine who have limited budgets, and it is a tragedy if they go and buy very expensive drugs—and I have actually been involved in the Eastern Mediterranean region on antibiotic policy—when they do not have penicillin there for the people because they run out of penicillin and start using more and more expensive drugs. So through the discussion of local needs you can then spend money more appropriately. The trouble with developing countries often is (a) there is so little money for most of the people and (b) there is a big private sector and often the private sector distorts the whole issue because there is a belief that if it is expensive it must be better and therefore "I must have". That is a terribly difficult issue. The WHO Programme has that difficulty but in Zimbabwe and Bangladesh it has been successful where there is more, if you like, strength and backing for the list as opposed to where there is a free market where it gets very complicated. So I do not think we should be re-inventing wheels in different places, we should be taking best practice from Australia or anywhere that demonstrates good practice and give that "Aunt Sally" to each nation and say, "Take it forward and tell us how you can best manage your resources." I do not believe you need more money necessarily until you have proven you are using wisely the money you are given. There is evidence in some countries that drugs are purchased for reasons which are not entirely straightforward. I will say no more.

670. Do you target individual diseases, say, in a refugee camp?

(Professor Petrie) What happened there was that there was a series of invited presentations across more or less each of the British National Formulary categories. There was then a debate by the local people and so, yes, we went through the lists for over a week and had a debate. There are major political issues in all of these cases, but, yes we do.

671. Is there somebody monitoring that they take their drugs for, say, tuberculosis?

(Professor Petrie) Dr Grimshaw has not told you that he is also the Director of the Effective Professional Practice Programme in the United

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Kingdom, which is a very big programme for doing just what you are saying, and he has conducted a major review on this.

(*Dr Grimshaw*) I will preface what I say by stating that I am quoting work undertaken by the Infectious Diseases Cochrane Review Group which has made a systematic review of interventions to try and improve tuberculosis compliance. They found a number of different interventions which can improve compliance with TB. Directly observed therapy (DOT), interestingly enough, has not been subject to a specific randomised trial, so although it is a policy in many areas we do not have good evidence that it is effective. I am working with colleagues in South Africa in the Western Cape where there is a major problem with TB compliance, and they are moving towards trying to find ways of educating clinic staff about how to ensure directly observed therapy works. One of their concerns is that DOT becomes a punitive action rather than a therapeutic alliance between the patient and the health care professionals. So I think that DOT will be a useful part of the broader strategy which will treat patients as partners in taking their medication.

Lord Rea

672. Could you please tell us more about your work on the implementation strategies for prudent prescribing practice? I think we lost a thread which was going towards evidence for the effectiveness of strategies used in changing in the right direction. Then, at the other end of the spectrum, I do not think we discussed in detail what happens when somebody from one of your research teams goes and talks to the individual doctors in the practice? How does it work at that end of the spectrum?

(*Professor Petrie*) The drug formulary which we produce is given to all undergraduates from third year upwards, so they will learn from that limited list, and that is a great help because we are talking of 150 drugs compared to, say, 3,000 or 4,000 in other systems. By participating in the selection of drugs at a post-graduate level—all the specialists and general practitioners—they learn through participation, which is a good way of learning because we know didactic lectures are a bad way of learning. So education through participation is very important. We have mentioned the ward pharmacists, who we believe are very important because they follow the junior houseman around and just check them early on if there are departures from practice, and that is particularly helpful. As I said, we have the therapeutics committee monitoring utilisation and going out to areas of outliers, but perhaps Jeremy might like to follow that up?

(*Dr Grimshaw*) Baroness McFarlane indicated earlier that sending out guidelines or materials by themselves was unlikely to change behaviour. I preface these comments by saying that I think the production of guidelines and formularies are a necessary first step, for the reasons I mentioned earlier, but by themselves are probably insufficient to ensure that the type of changes in behaviour you are interested in will occur in practice. I think we are increasingly recognising this

and looking to more active dissemination strategies. There is an increasing body of international literature from rigorous studies on how to change professional behaviour in prescribing and other areas, and this is currently being summarised by the Cochrane Collaboration on Effective Professional Practice, of which I am the co-ordinating editor. It is really the evidence from a series of systematic reviews done by over 100 researchers in eleven countries which I would like to present as evidence in terms of the relative effectiveness of different strategies. I am not at this point in time specifically disentangling prescribing from other behaviours, because I think there are some general issues across different professional behaviours which these interventions address. At the moment there are reviews completed on passive dissemination of educational materials, educational workshops, audit and feedback, educational outreach, local opinion leaders, extended roles of pharmacists, interventions to improve patient compliance with treatments, and mass media campaigns. There is a substantial body of information which is there and available to the Health Service in the United Kingdom. There has also been a very broad review of interventions to improve prescribing undertaken by Dr Paramjit Gill, who is a senior lecturer in the Department of General Practice in Birmingham, and there are a number of other reviews ongoing. What we know from this body of work is that largely ineffective interventions include the passive dissemination of educational materials. If the Grampian Formulary had been developed without all the other educational activities Professor Petrie has mentioned, my prediction would be that it would have been less effective than it has been, and again Dr McGavock mentioned other educational experiences happening around the COMPASS initiative which were trying to take these things forward. On didactic educational workshops and conferences, again there seem to be quite clear messages that if you go to a conference or a lecture it is unlikely to lead to changes in behaviour. It may lead to changes in knowledge but not behaviour. But interactive workshops, where you discuss things, where you can discuss some of the reasons why people prescribe and ways round that, do appear to be effective. Interventions of variable effectiveness include audit and feedback, although that does appear to be effective with respect to prescribing. However it is fair to say that you will only see modest changes of perhaps 10 to 15 per cent in absolute terms. So one of my comments on Dr McGavock's discussion earlier is that the £28 million saving would only be achieved with 100 per cent compliance, but in reality that type of intervention will only shift behaviour to a certain extent. So we need to be realistic about what these different interventions can provide. The use of local opinion leaders is a much-touted intervention at the moment in the United Kingdom, and again there is very variable information about their effectiveness and I would not recommend their use without further research at this point in time. More effective interventions include educational outreach. This is where you have a professional, often a pharmacist, going to visit a general practice or hospital to give a number of very selective messages about good

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prescribing behaviour which often use the marketing techniques of the pharmaceutical industry, to try and identify the specific barriers to the behaviour they want to happen, and modify their message based on these barriers and reinforce that message throughout that contact. I notice in your visit to America you met Professor Avorn, and really Professor Avorn and Professor Soumerai in Boston are the researchers on the effectiveness of that intervention. It is worthwhile saying that there is an ongoing large scale trial of educational outreach in the United Kingdom funded by the Department of Health, which should report over the next two years. So although it looks very promising, we should have much better information in the next two years about how useful this intervention is likely to be in United Kingdom settings. Multi-faceted interventions are often needed because we have several barriers to change, and also mass media campaigns are effective. One thing to note is that the cost effectiveness of these different approaches has not been currently established. So whilst we can say what interventions are effective, we do not know their cost effectiveness. I often say in talks, "If you give me £1 million, I will sort out your prescribing system in your hospital", but no one is ever going to give you £1 million, so we have to work out the efficiency of these interventions so we can have the best use of resources to ensure the intervention you use will achieve the change you want. There is a substantive NHS R&D programme on evaluating methods to promote the implementation of research findings which will feed into our knowledge of this. Up until now most of the evidence is North American but the United Kingdom is rapidly catching up. In conclusion, when considering behaviour change in general, there are no magic bullets. The particular interventions which should be chosen, depend on the targeted behaviour, the perceived barriers to the implementation (and these may be different in general practice and hospital settings, so you may need to consider different interventions across those) and local factors, which may include the resources you have got. But interventions of particular promise do include audit and feedback and educational outreach, and I think they could be used in the United Kingdom at this point in time.

Lord Rea

673. Earlier we were hearing about how important it is to influence patient expectations and educate the people who are receiving the prescriptions. I think you have been doing some work on patient education.

(Dr McGavock) My Lord, I had the privilege of sitting for 18 months on the National Working Party on Compliance with Medication, which was sponsored by the Royal Pharmaceutical Society and the Merck, Sharp, Dohme Foundation. I think its final report, entitled 'From Compliance to Concordance' of February this year would inform your Lordships better than any words of mine. I did the review of literature for that Working Party and the general consensus of all the many research efforts, mostly in America but some in this country, is that about 40 per cent of

patients do not take their medicines well enough to achieve any short or long-term benefits. The tip of the iceberg is that 40 per cent of all end-stage hypertension is due to non-compliance; 50 to 60 per cent of all end-stage diabetes—end-stage meaning of course death—is due to non-compliance with medication or diet; 70 per cent of end-stage glaucoma, ie blindness, is due to non-compliance; 91 per cent of all organ rejection in heart and kidney transplant patients is due to non-compliance. The same thing applies to antimicrobials. All the evidence is that without intervention at least 40 per cent of patients, or mothers if it is a child who is the patient, take the antimicrobial long enough for the patient to jump up out of bed and start running around and then stop. This may well be one of the most important factors in damaging antimicrobial power.

(Professor Petrie) Briefly four points. One in regard to patients. We have experienced huge difficulties in devising materials that patients can understand. I am advised that their reading age is about 9. My friend in the *Scotsman*, the medical correspondent, cannot write for patients and we are recruiting people from tabloid newspapers.

674. And the Scottish education system is better than ours!

(Professor Petrie) Even with the Scottish education system! So it is a real problem. I think Government has a problem in making evidence-based medicine too explicit because of the possible costs until we sort out the ineffective practice. The Scottish Office now in the new White Paper is making real efforts to engage the patients. The plea I would make to you is that in doing the SIGN process and the formulary process it is the economics, which was raised earlier, which is the real difficulty. We are short on pharmaco-economics. I know you have heard Peter Davey, and there is an Australian initiative, but it would be really helpful to get the true cost of antibiotics against the whole process of care, and any help in that direction would be very helpful. The second thing is to comment before we close on the legal situation of guidelines. We have just had a two-day conference with very senior legal opinion involved, and guidelines are not a threat because they are only like an editorial or anything else, and there are some very important legal tests—the "Bolam" test, and the test in England, the "Hunter" test—where if you have two or three other people who agree with what you are doing, in law you are okay. I would be happy to deposit that paper with you by Dr Pamela Abernethy, which is an updated review of the legal status of guidelines. That is why statutory guidelines on individual conditions are not on, because each doctor is an individual and each patient is an individual, and the circumstances are individual. The law in this country seems to be very reassuring on these points. Guidelines are not helpful to bad doctors, in the sense that if a lot of people have agreed on a course of action and you are the only man behaving in a very ectopic way, then your defence is much less good. But that surely must be good for patients. My last point is that I said we gave the formulary to all

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students, we also give the SIGN guidelines to all students in Scotland, so it forms part of their core knowledge, because they represent the future. If there were some authoritative antibiotic guidelines, that might be helpful to change behaviour, because the young are easier to change than the old perhaps.

(Dr Grimshaw) On the specific point about managing patients' expectations, I think there is an issue about managing doctors' perceptions of patients' expectations. If you ask patients what they want when they go into a consultation and then ask the doctor what they think patients want, there is often a mismatch. So although doctors will claim that patient pressure is a reason for prescribing, there is often this mismatch of perceptions which we need to address. This is about educating doctors in communication skills to listen to the patients' agenda and negotiate with them. Another related issue might be to let doctors know the likely impact of prescribing antimicrobials for minor infections. There has been recent randomised trial evidence that if GPs give antibiotics to patients, they are more likely to reattend if they have a similar complaint, so it is a false saving of time because basically these patients keep attending rather than being told, "You have a cold, you do not need antibiotics." There are interventions that address patients' expectations and again it looks as though you have seen examples of those in America. There is a growing body of information that mass media and patient information leaflets giving ideas about the benefits and potential harms of treatments are useful in terms of informing patients about what to expect from a consultation with a doctor.

Lord Perry of Walton

675. Dr McGavock, you suggested that the poor compliance in the case of antimicrobials might be a major factor in exacerbating drug resistant strains, and I very much agree with you. The question I want to put to both the Northern Ireland side and the Scottish side is, do your studies with general practitioners show any evidence whatsoever about the increases that are occurring in drug resistance?

(Dr McGavock) We have no studies on that topic in Northern Ireland, but the international consensus, such as for example a leading article in *The Lancet* earlier this year, indicates that the development of antimicrobial pathogenic resistance is strongly related to the volume of antimicrobial use, and that is as much as one can say. When one reduces the overall use of one antimicrobial, the resistance to that dies off for good microbiological reasons. That is as far as I could take it.

(Professor Petrie) I introduced myself by saying I am not an expert on antibiotics, but on this whole business of the evidence one of our Master's students last year looked at the change in prescribing behaviour in our area, comparing 1992-93 with 1995-96. There were huge changes in the behaviour of doctors in prescribing across ten drug groups. Sadly we did not study antibiotics as one of the test groups, but there is clear change in drug use. We have not done a study,

and we no doubt could do a study, on antibiotic resistance.

Baroness Platt of Writtle

676. How far do cultural, social and ethnic factors affect the attitudes to antimicrobials of practitioners and patients? Following on what you said earlier about patients not understanding advice because they have a reading age of 9, I wonder what the effect of gender is? Because very often it is the mother who is going to make sure the child takes what has been prescribed. When you said you were taking advice from tabloids, it might be a very good idea to put easily understandable advice in women's magazines.

(Dr McGavock) In the supplementary document which I will leave with your Lordships on our work on perceived morbidity and the prescribing response, we investigated all of these factors, including sex, age, certainty of diagnosis, diagnosis itself and a variety of other things. In fact sex is not a determinant of antimicrobial prescribing—

677. No, I am sorry, I meant from the point of view of the mother of the patient. I did not mean in terms of doctors.

(Dr McGavock) Professor Petrie referred to Dr John Howie's work of many years ago—27 years ago—and how he was able to associate statistically the prescribing of antimicrobials to children and prescribing of sedatives to their mothers. However, these statistical relationships must be treated with great suspicion and would be nowadays. It was a straw in the wind and there is no doubt about it, patient education must play a part and television and the media can do this if we really want to modify this. I do not know whether you want to go as far as warning parents or people that antimicrobials have risks as well as benefits and one of those risks is death. It is a fine balance which I am not competent to make but it can be done. I am sure it is very important to know that Johnnie or Joanna would be much better with a paracetamol linctus and a sore ear for two or three days and then come back and see me and if necessary then I will prescribe an antibiotic, knowing quite well that to see the patient in two days' time may well prevent having to see the same patient in four weeks' time with a recurrence.

(Professor Petrie) Briefly, the work by Professor John Howie on the social and cultural pictures has not been improved upon and he certainly presented it recently to the SIGN tonsillectomy group as one of the key factors in prescribing behaviour. I think you know that the Government is concerned with deprivation and there is no doubt that people who most need the care are the least likely to get it and we need to target that care very much better. It is like bone densitometry in the prevention of osteoporosis, the well ladies who are very healthy and well fed come for it, but the ladies who never see the sun mostly do not come for it. I suspect it is the same in all these strategies, we need to get to these deprived people who often have some of the factors you are suggesting. So it is a local thing, to target it by the health authority, say, "That is the

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[Continued

[Baroness Platt of Writtle Contd]

area" and go in there with a specific targeted message which would be inappropriate in another part of the town or country.

Lord Rea

678. I found as a practising GP that you could do quite a bit of health education with patients who had upper respiratory infections, and I am rather pleased to see that your findings confirm that you should perhaps give a patient a prescription for an antibiotic and say, "Hold onto that, if you are not better in two days then go and have it dispensed." The paper from the Southampton team shows that people who were given a delayed prescription were the ones who came back least. It could be they developed some better immunity than the others, or it could simply be that you got the patients to collaborate in the treatment plan?

(*Dr McGavock*) This, I am sure, is a most important point. Changing behaviour is important, as you say, and not just for doctors but for patients. It is difficult to do it but it can be done. Studies in Holland have shown how, using practice nurses, patients can have their behaviour changed in their expectation of medication for coughs, for gastroenteritis, for a variety of things. This is why I am in some ways very sad that my unit is being closed because your Lordships will have seen the prescribing jigsaw we produced and we believe that this bears a strong relationship to reality and indeed the factors with the asterisks we have quantified to well beyond statistical dispute. On the left hand side you will see the whole problem of the use of drugs as symbols, symbols of sympathy or concern or hope, symbols legitimising illness, terminating consultation. My colleagues, Dr Britten and Professor Weinman, at Guy's and Thomas' have begun to look at the whole business of symbolic use of medicines, patients' attitudes, beliefs, knowledge. This area must be researched if we are to understand what is going on in order to be able to do something about it, and I do think that drug use research units, wherever they are located, are essential to this process and should be continued.

Lord Jenkin of Roding

679. Could you tell us what happens to continuing medical education in Scotland? Does that include education for the prudent use of antimicrobials?

(*Professor Petrie*) As I have indicated, I think we can do a lot better, but through, if you like, the development of generic therapeutic schemes which look at drug utilisation. You can then get those doctors responsible for the antibiotic therapy guidance and formulary recommendations to go out and do continuing medical education around that area. Given Jeremy's point that lectures are not the best way to do it, it is more to do with the selection of these drugs. So if you have, as we have, 100 GPs representing different practices, they can participate and take the messages home. That is the way it is happening, rather than through formal lectures. Again, visits by the medical prescribing adviser, who goes round looking at the spends and the utilisation; and the pharmacy

practice adviser, which most health boards have now, who monitor utilisation and spend; these are terribly helpful to educate people as to what they should be doing rather than having them sitting asleep at a meeting and being given points for continuing medical education.

Lord Perry of Walton

680. Does this sort of discussion clash with what they are getting from the drug representatives?

(*Professor Petrie*) I am afraid it does. The drug representatives are far more effective than the academic educators are, as you know.

Baroness Masham of Ilton

681. Do you think there should be more education in teaching doctors how to communicate with patients? Some doctors treat the average patient as rather a stupid person, and actually patients are not stupid if they are treated in the right way. I have talked to prisoners and they are very receptive if they think it is going to help.

(*Professor Petrie*) I think your Lordships will be aware of the huge initiative by the General Medical Council to disassemble the baronies of specialties and to emphasise communication skills right from the beginning of the undergraduate medical curriculum course and throughout the course. We regret that students are getting less teaching on pharmacology and clinical pharmacology and therapeutics, but they are getting a lot of teaching in communication skills. Particularly in primary care there is great emphasis on communication skills nowadays, but we are talking about generations moving through.

(*Dr Grimshaw*) I would agree with what Professor Petrie has said. It continues into the post-graduate education setting. There has been evidence that we can teach post-graduates to be better communicators leading to better patient outcomes, and there are several trials which show that. I think both are needed and it is a learning process which should continue throughout the professional's life.

(*Dr McGavock*) To extend that, can I say it is my opinion a great deal more time needs to be given at the undergraduate level to teaching both pharmacology and therapeutics but especially to the teaching of microbiology, perhaps at the expense of subjects such as pathology, which gets approximately 300 hours' teaching time, and anatomy, which gets about 300 hours' teaching time.

682. The surgeons would be jumping up and down!

(*Dr McGavock*) Anatomy and Physiology are important but perhaps in the modern world less important than the scientific principles underlying drug use, especially in antimicrobials.

Chairman

683. As you know, we have recently visited the USA and you have seen a note of our report on that about education for the prudent use of antimicrobials.

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[Continued

[Chairman Contd]

What approaches noted in that memorandum have been tried here, and to what effect?

(Dr Grimshaw) I think I have covered a lot of the interventions in my presentation. Briefly, in paragraph 61 you allude to mass media campaigns to reduce red meat consumption. There is evidence in general those campaigns are effective but are only likely to result in small to modest changes. Just to reiterate, we often need several things to happen to get the sea change you are interested in. In paragraph 66, we have discussed briefly the issues about whether it is quicker to prescribe or not, and I think we have good randomised trial evidence from the Southampton group that not prescribing may reduce reattendance which Lord Rea raised. At the end of that paragraph you mention CDC training senior doctors to disseminate the concepts and materials to their peers, and I think this is still a largely unproven technique. There are six randomised trials using so-called local opinion leaders, none of which are based in the United Kingdom, and we are currently conducting a study where we are finding it difficult to find educationally influential GPs in the United Kingdom setting, although we can find them in hospital settings such as surgeons. So I think this is one intervention we would need to be cautious about. When you saw Dr Avorn he mentioned educational outreach visits and that is probably the intervention where there is strongest evidence of effectiveness, but we need to see how generalisable that is to the United Kingdom setting. There are several on-going trials which will provide useful information. We also potentially have resources in the system through the medical prescribing advisers to provide that intervention. A model is being tested in a project in York and London involving medical prescribing advisers using educational outreach methods to see if they can better get their messages across. I would be happy to provide contact details for

that study if it was helpful. Likewise on patient placebos, there is growing evidence of their effectiveness. All of these things are additive, and we will probably need a combination of several of these things to achieve the change you want.

684. Finally, what success stories can we quote in this country?

(Professor Petrie) Talking about the SIGN initiative, first of all, I have mentioned the effect of the SIGN *Helicobacter* guideline. I could give you a catalogue of things which are not related to antibiotics apart from that. The SIGN tonsillectomy programme is already influencing behaviour because the SIGN group have had a national meeting and they are coming to a view before the guideline is even published. There will be evidence particularly on base lines and there will be follow-ups, and we can certainly provide the evidence to you. In terms of the drug formularies, I have demonstrated to you the changes in the prescribing behaviour and we have looked at antibiotics in particular in terms of coincidence with the formulary, and it is really quite remarkable. I mentioned 90-96 per cent earlier and that is quite a remarkable ownership of the local policies. General practitioners do not wish to be "outliers", they wish to be part of the herd. They do not want to be exposed and fined. If you give them an anonymised A, B, C, D list of what they are doing in their respective practices, how many are they using and what drugs are they using, and nobody else is using it, Professor Howie showed that people tend to move into the middle of the usage range. I think this ownership and behaviour change and audit and feedback are helpful, plus all the other interventions we have mentioned.

(Dr McGavock) Certainly in Northern Ireland the COMPASS system works, but only works really well if it is done by a prescribing adviser on prescribing visits and if there is an incentive.

Chairman] Gentlemen, thank you very much.

Supplementary Memorandum by Dr H McGavock

I wish first to express my appreciation for the detailed hearing your committee gave my evidence yesterday. I regard it as a great privilege to have been invited to attend.

Second, although I did not wish to contradict my friend and respected colleague, Professor James Petrie, I was strongly opposed to his suggestion that antibiotic use by general practitioners will be significantly ameliorated by agreement and discussion. Having spent 12 years as a GP and a further 17 years researching the behavioural phenomena which underly general practice prescribing, coupled with well over 2000 face-to-face visits to general practitioners to seek an improvement in the rationality of their prescribing, I am probably a more expert witness on this topic than most people in the UK. The purpose of this letter is to urge your committee to consider very seriously my suggestion of statutory regulation of GP antibiotic use. At its simplest, this could take the form of statutory classification of certain antibiotics as "*hospital use only*". At present, that would include the antibiotics: co-amoxiclav, ciprofloxacin, norfloxacin, ofloxacin, clarithromycin, azithromycin.

If your committee recommends the voluntary self-regulation approach, it will be tinkering around the edges of this very serious problem facing the nation. Certainly, a proportion of GPs would abide by the guidelines in Table 1 of the British National Formulary, or those in the Practice Formulary of the Royal College of General Practitioners (which we produce in Belfast for the national college, a copy of which I left with Mr. Makower yesterday). The bulk of the frequency distribution curve of general practitioners would partially implement the guidelines and a substantial proportion on the other side of the frequency distribution curve would ignore them

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completely. The result would be a limited improvement in antimicrobial resistance, which is not what is required if we are to preserve the antimicrobial era. A direct parallel would be that in this battle for the antimicrobial era some of the army would obey the general's instructions to the letter, some would obey those parts of the instructions which suited them, and a significant proportion of the army would ignore the instructions altogether!

General practitioners are among the most independent-minded of professionals, accustomed to trusting their own judgement and experience and our research in Belfast has shown how wide the variation in *modus operandi* is, no matter what parameter one selects. Hospital physicians and surgeons are a great deal more amenable to consensus decisions, and it is with this group that Professor Petrie has most experience.

Finally, if I can assist your Lordships further in any way, my time, experience and our team research results are at your disposal.

Dr H McGavock

Director

18 December 1997

Supplementary Memorandum by Dr Jeremy Grimshaw

FURTHER EVIDENCE ON INTERVENTIONS TO IMPROVE HEALTH CARE PROFESSIONAL— PATIENT COMMUNICATION IN ORDER TO PROMOTE APPROPRIATE ANTIMICROBIAL PRESCRIBING

BACKGROUND

- Doctors frequently state that patient pressure is a key determinant of inappropriate antibiotic prescribing, especially in primary care settings. Whilst this is probably is an important factor, there is evidence that doctors overestimate patient's expectations of receiving prescriptions (Britten 1997).
- Prescribing antimicrobials for minor self limiting illnesses increases patient's expectations and likelihood of receiving similar treatment if symptoms recur (Greenhaugh 1997; Little 1997).
- A patient centred approach would potentially address some of the problems associated with inappropriate antimicrobial prescribing (Laine 199x).

HEALTH CARE PROFESSIONALS' EDUCATIONAL NEEDS

- Some health care professionals overestimate the extent to which they communicate with patients about prescription medicine (Makoul 199x).
- Health care professionals' communication skills can be improved through continuing professional education.
- Interventions of particular promise include interactive workshops with opportunity to practice desired behaviours (Thompson 1998).
- Educational activities should encourage a patient centred approach, focusing on methods of eliciting patient's beliefs and expectations and addressing patient's expectations when inappropriate.

PATIENT AND PUBLIC EDUCATIONAL NEEDS

- Patient's beliefs and expectations can be modified through general interventions at the population level and specific interventions during health care professional—patient interactions.
- Mass media campaigns are effective interventions to modify health care utilisation (e.g., attendances for minor illness) (Grilli 1998).
- Patient information leaflets and information giving in health care professional-patient interactions can be effective, especially if these address patients' existing beliefs and expectations (which vary across different areas, socio economic groups and cultures) (Entwistle 199x).

SUMMARY

- Patients' expectations or doctors' perceptions of patients' expectations may influence inappropriate antimicrobial prescriptions especially for minor self limiting illnesses.

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- Multi faceted interventions targeted at professionals, general public and patients are likely to be needed to address this problem.

Dr Jeremy Grimshaw, Programme Director, Health Services Research Unit, University of Aberdeen.

Dr Vikki Entwistle, Research Fellow, NHS Centre for Reviews and Dissemination, University of York.

References

Britten N, Ukoumunne O (1997). The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: questionnaire study. *BMJ*, 315, 1506-1510.

Entwistle VA, Watt IS, Davis H, Dickson R, Pickard D, Rosser J. Developing information materials to present the findings of technology assessments to consumers: the experience of the NHS Centre for Reviews and Dissemination. *International Journal of Technology Assessment in Health Care*, 14 (*in press*)

Greenhaugh T, Gill P (1997). Pressure to prescribe. Involved a complex interplay of factors. *BMJ*, 315, 1482-1483.

Grilli R, Minozzi S, Freemantle N, Domenighetti GF, Finer D (1998). The impact of mass media campaigns on health services utilisation and health care outcomes. In: *The Cochrane Library* [database on disk and CDROM], issue 1. Oxford: Update Software.

Laine C, Davidoff F (1996). Patient-centered medicine: a professional evolution. *JAMA*, 275, 152-156.

Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmouth AL (1997). Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ*, 315, 350-352.

Makoul G, Arntson P, Schofield T (1995). Health promotion in primary care: physician-patient communication and decision-making about prescription medications. *Social Science and Medicine*, 41, 1241-1254.

Thomson MA, Freemantle N, Wolf F, Davis D, Oxman AD (1988). Educational meetings, workshops and preceptorships to improve the practice of health professionals and health care outcomes. In: *The Cochrane Library* [database on disk and CDROM], issue 1. Oxford: Update Software.

TUESDAY 20 JANUARY 1998

Present:

Dixon-Smith, L.	Rea, L.
Gregson, L.	Soulsby of Swaffham Prior, L.
Jenkin of Roding, L.	(Chairman)
Masham of Ilton, B.	Walton of Detchant, L.
McFarlane of Llandaff, B.	
Platt of Writtle, B.	Phillips of Ellesmere, L.
Porter of Luddenham, L.	

Memorandum by the Wellcome Trust

THE WELLCOME TRUST'S RESPONSE TO THE GLOBAL RISE IN DRUG RESISTANCE

1. Over the past five years the Trust, responding to evidence from its scientific advisors, has become increasingly concerned about the rapid global rise in drug resistance in both parasites and bacteria. Of special concern is the development of drug resistance in agents causing severe human diseases such as malaria and tuberculosis. Consequently, the Trust has already responded to this escalating problem in two ways.

RAISING THE PUBLIC PROFILE OF ANTIBIOTIC RESISTANCE

2. One way in which the Trust is approaching this issue is by raising its public profile through scientific meetings and press conferences. To this end, a conference in the "Frontiers of Science" series was held in May 1997. The purpose of this meeting entitled "Antibiotic Resistant Bacteria: a Threat to International health" was to bring together a group of clinicians, clinical microbiologists, basic scientist, epidemiologists and veterinarians, all expert in different aspects of antibiotic usage, resistance mechanisms, molecular epidemiology, and the control of infections, to define the threats posed by antibiotic resistance in bacteria and to consider approaches to combat them.

3. The purpose of all concerned was to consider ways of reducing or overcoming the threats posed by antibiotic resistance, and various approaches to infection control. Policies for antibiotic usage were also examined, together with the contributions that mathematical modelling might provide to optimising antibiotic usage.

4. The inter-relation between antibiotic usage in man and animals was considered to be an essential aspect of any consideration of antibiotic resistance and this was debated in a series of presentations by veterinary, medical and industrial microbiologists. This subject has been debated at length through a recent "Electronic Discussion Group", organised by the WHO. A report from this group and the conference which followed it will be published shortly by the WHO.

5. All participants in the Trust Frontier Conference concluded that this was the time to review the problem of antimicrobial resistance as a global problem. Resistance affects all countries and societies, from the most advanced Western societies with complex and high technology medical services, to the poorest countries where medical services struggle with such basic inadequacies as contaminated or inadequate water supplies and gross overcrowding. Everywhere, the hospital and the general community exchange resistant organisms, and international travel creates a "global village" for the bacteria as well as their human hosts. Not only does resistance make treatment more difficult and expensive, the truly untreatable infections have arrived in the form of multi-resistant tuberculosis, vancomycin- and methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci in Japan.

6. A copy of the full report from this conference is attached (Appendix A), and the main issues discussed in an article in Wellcome News (Appendix B) (*not printed*).

7. Immediately following the meeting, the Trust held a press conference and several conference delegates representing the Trust, the pharmaceutical industry, the Public Health Laboratory Service (PHLS) and research scientists and infection disease clinicians from the UK and overseas were present. The main conclusions of the conference were presented and are summarised as follows:

- Surveillance in several countries has revealed a rise in infections caused by antibiotic-resistant bacteria, not only in the general population in a number of countries, but also in hospitals and managed-care facilities, such as nursing homes and day-care centres. This rise appears to be linked to increased use of antibiotics and/or inadequate infection control measures.
- Uninformed drug prescribing practices by GPs and demands from their patients may be linked to an increase in drug-resistant bacteria.

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- A recent study by the PHLS indicated that there is a 7 per cent chance of acquiring a bacterial infection during a stay in hospital in the UK. If methicillin-resistant bacteria also acquire resistance to vancomycin, many of these hospital-acquired infections will become untreatable.
- Some pathogenic bacteria are now resistant to all commonly used antibiotics. In addition, some aggressive pathogens are resistant to powerful antibiotics such as methicillin and vancomycin. There is now evidence from studies in Japan that aggressive pathogenic bacteria are acquiring resistance to both methicillin and vancomycin resulting in untreatable, fatal infections.
- The widespread prophylactic use of antibiotics in animal husbandry may contribute to antibiotic resistance in human pathogens.
- Uncontrolled over-the-counter sales of antibiotics in several countries is associated with the rapid rise in antibiotic resistant bacteria in those countries. This situation is frequently exacerbated where the majority of the population is too poor to afford the most appropriate treatment and health authorities have insufficient resources for infection control.
- The high cost (up to £300 million) and the long delays (up to 15 years) in bringing new drugs to the market, coupled with increasing levels of global antibiotic resistance, is resulting in a widening gap between the appearance of novel drug-resistant pathogens and our ability to deal with them.
- The rapid rise in international travel means that any drug resistant bacteria appearing in any part of the world can appear in North America and Europe within 24 hours.
- There is an urgent need for increased surveillance for antibiotic-resistant bacteria, both at the national and international level, linked to antibiotic use and clinical outcome.
- New research tools and technologies have shown that the genes conferring antibiotic resistance are easily and frequently transmitted between bacteria, and resistant bacteria move rapidly between human populations.

THE ESTABLISHMENT OF A PATHOGEN GENOME SEQUENCING CENTRE AT THE WELLCOME TRUST GENOME CAMPUS, HINXTON, CAMBRIDGE

8. In 1995, the Trust decided to examine the utility of the new technologies of rapid genome sequencing, to accelerate research in microbial and parasitic diseases. These technologies speedily provide the complete genetic “code” which determines every structure and function of a micro-organism. Of special interest was the possibility of obtaining the complete genomic information of important bacterial pathogens within a short space of time. Thus, instead of the handful of drug and vaccine targets currently available to researchers and the pharmaceutical industry, many thousands of conventional and novel therapies could be developed. Furthermore, drug targets which are less susceptible to the induction of resistance could be identified, as well as those which are common to many species of bacteria.

9. To this end, the Trust dedicated one of its conferences in the “Frontiers of Science” series to “Sequencing of Bacterial Genomes”. At this Conference (held in April 1995), Dr Craig Venter from The Institute for Genomic Research presented, for the first time, the complete genetic code of the genomes of *Haemophilus influenza* and *Mycoplasma genitalium*. The substantial and rapid progress that could be made in understanding the basic biology of these organisms, their mechanisms of pathogenesis and the identity of new vaccine and drug targets became immediately obvious to all participants at that meeting. Following the subsequent publication of this information, the infectious diseases research communities have become excited by the possibility of obtaining the complete genetic code of several bacterial and parasitic pathogens and the substantial advances that could be made both in basic biology and the control of human and veterinary infectious diseases. Feelings in the scientific community were accurately summarised in a Nature “News and Views” article by Professor Barry Bloom of the Rockefeller University, New York.

“The power and cost-effectiveness of modern genome sequencing technology mean that complete genome sequences of 25 of the major bacterial and parasitic pathogens could be available within five years. For about 100 million dollars, we could buy the sequence of every virulence determinant, every protein antigen and every drug target. It would represent for each pathogen a one time investment from which the information derived would be available to all scientists for all time. And we could then think about a new, post-genomic era of microbe biology”.

10. Consequently, the Governors of the Trust agreed to provide up to £18 million to establish a Pathogen Genome Sequencing Centre at the Wellcome Trust Genome Campus, Hinxton, under the leadership of Dr Bart Barrell. In February 1996, the Governors agreed to provide a grant of £1,232,642 to Dr Barrell in collaboration with Dr Chris Newbold (University of Oxford) and Dr Stuart Cole (Institute Pasteur, Paris) to sequence the complete genome of *Mycobacterium tuberculosis* (TB) and chromosome 3 of *Plasmodium falciparum* (malaria). An additional grant of FF500,000 was awarded to the Institute Pasteur to support the analysis of the TB genome.

11. The complete genetic code of the TB bacterium was published by the Sanger Centre on their Website on 16 December 1997. The publication of the complete nucleotide sequence of chromosome 3 from the malaria parasite is also expected very soon.

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12. In 1997, the Trust gave additional funds to the Sanger Centre to determine the genetic code of *Neisseria meningitidis* (a major cause of bacterial meningitis), and over half that of the malaria parasite. The grant of £675,000 to sequence *Neisseria meningitidis* was in collaboration with Professor Brian Spratt of the University of Surrey, and the grant of £5.7 million to sequence half the genome of the malaria parasite was given in collaboration with Dr C Newbold of Oxford University. The Trust's support for malaria genome sequencing is the largest single contribution in an international consortium of funding bodies, dedicated to completing the entire genome sequence of the malaria parasite. The other members of this consortium are the Burroughs Wellcome Fund, the National Institute of Allergy and Infectious Diseases, and the US Department of Defense.

13. It is intended to co-ordinate the Trust's future activities in this area through its company "Beowulf Genomics" (see below), and funds have been set aside for work on *Campylobacter* (a major cause of food poisoning) and *Candida* (a fungal infection associated with AIDS).

CO-ORDINATION OF SURVEILLANCE

14. A major weapon in tackling the problem of antibiotic resistance is the establishment and maintenance of reliable and comprehensive surveillance. The Trust is contributing to this in several ways. Trust staff have had several meetings with Professor Richard Wise and Professor Alistair McGowan of the British Society for Antimicrobial Chemotherapy about the establishment of a nationwide surveillance programme. It is intended that this initiative be co-ordinated with recent activity by the PHLS in the establishment of a antimicrobial reference unit. The Trust is assisting the work of the PHLS in this area in other ways, mainly by encouraging collaborative research with strong academic centres and by providing research training for young clinical microbiologists.

RECENT WELLCOME TRUST SUPPORT FOR MICROBIAL RESEARCH

15. The Wellcome Trust has supported both basic and clinical research into microbial diseases for many years. Research scientists can apply to the Trust through a variety of schemes which include project grants (normally for three years), programme grants (normally for five years), personal fellowships, equipment grants, support for scientific meetings, and major applications for the refurbishment of research laboratories. In addition, the Trust has established a dedicated scheme of Research Fellowships in Medical Microbiology, designed to give young clinical microbiologists first-hand experience of fundamental research in high quality laboratories, both in the UK and overseas.

16. The Trust's support for research in this area over the past five years is summarised in the Table. This support is given mainly to universities in the United Kingdom and the Republic of Ireland, but overseas research, especially in tropical countries, also receives substantial funds.

17. Two examples of the Trust's support outside the UK are its support for the work of Professor Nick White in Vietnam, and Professor Bill Watkins at the Wellcome Trust Research Laboratories in Nairobi. In Vietnam, multi-drug resistance in *Salmonella typhi* (typhoid fever) has spread at an alarming rate, suggesting either powerful selective pressures from antibiotic use or, more recently, that multi-drug resistance may be associated with virulence directly (possibly by something else being transmitted on the resistance-carrying plasmid). They have also just found that Vietnam has either the highest, or the second highest, rate of resistance to pneumococcus in the world. The preliminary studies suggest that this rate is much higher in the urban areas, which would again point towards antibiotic use as a selective pressure. Professor Watkins is preparing to establish the East African Network to Monitor Antimicrobial Treatments (EANMAT). EANMAT is an initiative by experts in Tanzania, Kenya and Uganda to strengthen the regional information base on parasite drug sensitivity on which rational treatment policy and effective chemotherapy for malaria can be based in the three countries. The network has high level commitment and support within the Ministries of Health in the three countries. This joint initiative brings together not only the three national malaria control programmes but also other operational and research expertise, as part of a network, to provide a dynamic assessment of the situation through a credible national and regional network that could provide the necessary comparable data for improving malaria therapies; these are urgently needed for control of malaria in this region.

FUTURE ACTIVITIES BY THE WELLCOME TRUST

18. Apart from continuing to support research in university departments, the Trust is planning a number of initiatives to facilitate and accelerate the transfer of new drugs and vaccines from the laboratory to the clinic.

BEOWULF

19. The Wellcome Trust has been concerned for some time to ensure that the genome sequences of microbial pathogens were available to as wide a range of researchers as a possible. A significant number of microbial pathogens have been or are being sequenced by industrial companies in such a way as to prevent any publication of the genome sequence. Obviously if the sequence data are obtained and held so that there is no public access, the wider scientific community cannot benefit from them. This has a number of disadvantages. For example,

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experience with the human genome and with those microbial genomes which have been sequenced shows that access to the sequence data provides a tremendous incentive to further research. This is very important with microbial pathogens, in particular bacteria, given their increasing resistance to antibiotics. Equally, once a micro-organism is known to have been sequenced "in private", other groups are less willing to sequence it again, even if there is no prospect of the finished genome sequence ever being released for public use. Thus, although the commercial and unpublished sequencing of a micro-organism will bring some benefit to human health, greater benefit would accrue if the sequence were publicly available.

20. In order to assist in accelerating the pace of research into microbial pathogens, the Wellcome Trust has decided to fund the sequencing of a significant number of these genomes. The initiative, known as Beowulf, intends to support the sequencing of up to 10 microbial genomes at the Sanger Centre during 1998–99. The first two projects have already been approved. In all cases, the data will be made available free of charge to the scientific community. It is hoped that other organisations, including industrial concerns, will join in with the funding of the sequencing of microbial pathogens so that a co-ordinated approach can be taken internationally. The benefits to the scientific community of this in terms of general access to the data and in preventing unnecessary repetition of sequencing are considerable. In the longer term, these benefits will undoubtedly be experienced by all of mankind.

CATALYSIS BIOMEDICA

21. The Wellcome Trust plans to establish a subsidiary company to promote the development and application of biomedical science to advance human healthcare.

22. The new company will be charged with protecting and exploiting intellectual property arising from Trust-funded research, thereby ensuring that the fruits of the Trust's charitable research funding activities are developed for the public good. In practical terms, it will work with researchers and their institutions to identify and patent research of potential medical value, and will negotiate agreements with companies in the pharmaceutical and biotechnology sectors to turn such results into new products to improve human health.

23. The company also intends to manage a "development fund", which will be used to seed new start-up companies and to develop Trust-funded research in directions amenable to commercial exploitation. The work of the new company thus will follow through on the Trust's charitable mission, as set down by Sir Henry Wellcome in his will, to support research directed towards "improvement of the physical conditions of mankind".

24. Profits ultimately gained from this new venture will be channelled back into the Trust itself, to provide additional income for its philanthropic activities. The Trust will continue to fund research solely according to its scientific merit, not its potential commercial applicability.

ORPHAN DRUG INITIATIVE

25. The Trust is concerned that many pharmaceutical companies are unable to develop experimental drugs and vaccines whose use would be mainly in developing and restructuring countries. Consequently, the Trust is exploring the possibility of engaging with the public and private sectors in consortia to create initiatives for the development and manufacture of drugs and vaccines for infectious diseases in the developing world.

John R Stephenson PhD

Scientific Programme Manager

19 December 1997

Recent support for research in bacteriology

	Grants £	Personal support £	Symposia £	New buildings £	Equipment £	Tropical units £	Annual total £
1992–93	3,465,907	1,726,266	0	0	416,696	1,651,406	7,260,275
1993–94	5,550,056	3,625,319	3,500	0	393,069	1,804,404	11,376,348
1994–95	3,737,491	4,440,464	50,000	0	961,720	2,413,398	11,603,073
1995–96	11,428,615	5,304,537	48,000	0	3,083,333	3,492,458	23,356,943
1996–97	10,617,654	11,941,343	6,000	7,307,195	2,845,011	3,556,873	36,274,076
Total	34,799,723	27,037,929	107,500	7,307,195	7,699,829	12,918,539	89,870,715

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[Continued

Examination of witnesses

DR JOHN STEPHENSON, Scientific Programme Manager (Neuroscience), and PROFESSOR ROY ANDERSON, Director, Wellcome Trust Centre for the Epidemiology of Infectious Disease, University of Oxford and Governor of the Wellcome Trust, were called in and examined.

DR RICHARD BAX, Director and Vice-President, Anti-infective Therapeutic Unit, SmithKline Beecham Pharmaceuticals, was called in and examined.

Chairman

685. Gentlemen, thank you very much for coming here to present your evidence to our enquiry.

(*Professor Anderson*) Thank you, my Lord Chairman. I am Professor Roy Anderson and I represent the Wellcome Trust as a governor of the trust. I also wear an individual scientist's hat as someone who specialises in infectious disease epidemiology.

(*Dr Stephenson*) I am Dr John Stephenson. I am a programme manager for the Wellcome Trust. I have been responsible for much of the activities of the trust in the past years in this area.

(*Dr Bax*) I am Richard Bax, head of worldwide clinical development of antimicrobials for SmithKline Beecham. I have been in the industry for 20 years. Recently, I have been working very closely with Professor Roy Anderson and participated in the Wellcome Trust's meeting on bacterial resistance in May.

(*Professor Anderson*) May I be permitted to say a few words about the position of the Wellcome Trust?

686. Indeed.

(*Professor Anderson*) I am sure that many members of the Committee are familiar with the Wellcome Trust. It is the largest independent biomedical charity in the world and it supports three major areas of research into biomedicine. First, it supports career development; in other words, it supports at a very basic level the research training of graduates right the way through to support of very senior scientists at research professorial level. The second area of funding is major initiatives, such as the establishment of the sequencing centre at Hinxton Hall, Cambridge, and very large research facilities. Thirdly, it is a responsive funding organisation, like the Medical Research Council, in that it responds to requests from the community to support particular research projects. In the field of microbiology in general, from 1992 to the present we estimate that we have spent approximately £90 million in supporting this area of research. Of that sum, a very small fraction has been spent directly in the area of antibiotic resistance (perhaps less than 5 per cent). The reason for the bias is due largely to requests from the community; in other words, we have not received many requests from the scientific and biomedical community to support work in this area. However, we believe that by supporting basic scientific research and clinical research in microbiology we are adding to the pool of expertise in the United Kingdom that may contribute to examining antibiotic resistance. Looking at our current funding and interests, it is probable that

our support of the specific area of antibiotic resistance will rise over the next five years for a variety of reasons. First, we have been lead players in initiating pathogen genome sequencing projects. The first results of our support have been the complete sequencing of the bacterium that causes tuberculosis in humans which is one of the biggest, if not the biggest, global killer at the present time. We hope to sequence a whole series of bacterial genomes. We believe that such knowledge will lead to speedier progress in identifying genes as targets for drugs and to progress the very difficult area of the development of vaccines for bacterial pathogens. Secondly, we support basic scientific research on pathogenesis in the community in a responsive way, both clinically and scientifically. We have also taken an initiative in population genetics via our initiative to support research on Biodiversity. Sadly, this is a subject which is all too lacking in research in antibiotic resistance and yet it is key to it. Those who work in the field of antibiotic resistance broadly speaking are ignorant of the subject of population genetics, which is a fairly technical field. We are doing that via a biodiversity scheme to look at the diversity of bacterial organisms that afflict humans. Lastly, we have supported a small amount of epidemiological research into antibiotic resistance. We imagine that this will grow in the coming five years as the field of antibiotic resistance gains higher priority among the epidemiological community. We believe that the quality of epidemiological research in this area, not just in the United Kingdom but worldwide, is on average poor. There is a variety of reasons for this, some purely scientific—for example, the difficulty of studying genetically very diverse organisms with no clear immunological markers of present and past infection—but we feel that a lot more can be done in this area in terms of addressing questions ranging from simple sampling of bacteria to the design of community-based surveillance. Most patients are infected with drug-resistant and non-resistant susceptible organisms. To estimate the frequency of resistance is problematic straight off in the sampling of an individual patient. Thirdly, the quantity of epidemiological surveillance is extremely small. Worldwide, the number of quality longitudinal studies—meaning over time—of cohorts of patients, the rate at which they accumulate particular bacterial infections and knowledge as to where resistance lies in the community is very limited. Therefore, from the basic scientific research point of view we hope that the Wellcome Trust will be able to support initiatives in that area. That is a very brief outline of the activities of the Wellcome Trust.

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DR JOHN STEPHENSON, PROFESSOR ROY ANDERSON
and DR RICHARD BAX

[Continued

Baroness Masham of Ilton

687. Can Professor Anderson give a little further explanation of population genetics?

(*Professor Anderson*) A very fundamental concept in biology is the concept of evolution; in other words, selection of the fittest organism. This area has evolved into a particular subject in biology called evolutionary biology, a key component of which is the study of population genetics which is the attempt to quantify the selective pressures that cause changes in the frequency of different genes in populations and explain the genetic diversity that we see in populations today, how it evolved, why it is there and how it is likely to change in future. The very simplest example of antibiotic resistance is the following. The major selective pressure in determining the frequency of antibiotic resistance is the volume of drug use in a particular country, hospital or community. If you ask how many studies worldwide have quantified the frequency of drug resistance to a particular pathogen, and the volume of drug use which is the selective pressure, there are only three such detailed studies published at present, worldwide today: two in Finland and one in Iceland. Those studies have revealed a lot of interesting scientific points, but it is extraordinary that at this point of time our information is so limited. Population geneticists study selective pressures, which is the quantification of drug volume in the case of antibiotic resistance. That is a rather trivial explanation, but it is a field within evolutionary biology—and a key one is the study of the evolution and persistence of antibiotic resistance.

Chairman

688. Before we begin our questions, are there any other introductory comments?

(*Dr Bax*) Following Professor Anderson's explanation, currently there are more bacteria in or on us individually than the total human population of the world. That explains some of the complexities that we face.

689. You are undertaking collaborative work on surveillance of resistance with the Public Health Laboratory Service and BSAC. Implicit in this is the network of organisations such as NHS labs, the PHLS and so on, and yet we understand that you are more concerned to fund academic centres. How do you perceive such problems may be overcome?

(*Professor Anderson*) The governors of the trust have made the deliberate policy decision not to support Government-based research laboratories, for the reason—rightly or wrongly—that they feel that if they do they will be taking over the responsibility of the Government to fund research in the Public Health Laboratory Service. All of us feel slightly concerned about the decreasing volume of research which the PHLS has been able to support over the past 10 years. We believe that it is an outstanding service. To support quality surveillance in the United Kingdom there must be a strong research base. We believe that it is the responsibility of government to support that, not medical charities. However, in trying to be helpful last year we organised a dinner attended by the leading

microbiologists in the United Kingdom and the director of the PHLS. We discussed ways in which the Wellcome Trust might collaborate. From that emerged the notion that we would seek ways to see whether a research project could be funded within a university which had strong collaboration through the PHLS network. We would like to move that forward in 1998 to see whether we can choose a particular initiative and quality research centres which are university-based with strong links with the PHLS. That is the present policy. Policy is reviewed annually by the Trust.

Lord Jenkin of Roding

690. At the time that the very important White Paper *Realising our Potential* was prepared I led a delegation from the Association of Medical Research Charities to see the then Minister for Science, Mr William Waldegrave. I for one was mildly disappointed that when the document emerged it had only a small reference to the role of the medical charities. The reference was limited to one small paragraph. In the context of the question just asked about collaboration with the PHLS, do you feel that four or five years later there is now a better understanding of the complementary role of the charities than there was perhaps in the past?

(*Professor Anderson*) Very much so, in part because of the enormous growth of the Wellcome Trust due to the relatively recent sale of its shares in Burroughs Wellcome to Glaxo. As with other medical charities, the trust works very closely in collaboration with the Medical Research Council. We constantly discuss policy and try to support initiatives jointly and ensure there is no unnecessary overlap. I feel that today there is a very clear feeling that if you look at the relative spend on medical research between the Department of Health and the Medical Research Council and the large body of charities the latter contributes a very significant fraction of the total.

Lord Jenkin of Roding] This was not appreciated by the department some while back.

Lord Walton of Detchant

691. We have received an enormous mass of evidence from innumerable sources. It has made clear that most of the existing antibiotics, even those introduced in the past 10 to 20 years, have been derived from relatively minor modifications of earlier antibiotics most of which were derived from microbial sources, and progressively more and more resistance to each of the new ones has begun to emerge. It has been made clear to us that perhaps a new approach to other forms of antimicrobial agents is needed. For that reason I was interested to hear about your genome projects. We have received a lot of evidence from others, for example the Centre for Applied Microbiology, suggesting other novel approaches to the development of antimicrobial agents: bacteriophages, anti-bacterial peptides, proteins and others. Some of these are clearly related to your genome project and some are not. Where do you see

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[Continued

[Lord Walton of Detchant *Contd*]

the development of new antimicrobial agents coming from most quickly?

(*Professor Anderson*) If I knew I would probably be a wealthy man! My personal scientific view, not the view of the Trust, is that the genome projects that the Trust has supported will provide an enormous number of clues about potential target genes for drug and vaccine development. There is no doubt that this research will provide a lot of clues about whether the development of a vaccine is a feasible objective or whether the antigenic variation or variation of the bacterial antigens expressed on the surface is so large that to try to deal with such quickly moving targets is a waste of time. To give an illustration, in relation to the tuberculosis genome which came out just before Christmas one of the major antigens thought to be important in triggering immune responses has always been viewed as antigenically very constant. The new genome data suggests that there is a little hotspot of variation—and it may be that that is quite important in enhancing the persistence of mycobacterial infection not only in the individual patient but in the communities of people. The Wellcome Trust supports grant applications from scientists; however, as is always the case, it is difficult to predict which will be the most useful in an applied context in the future.

692. Antibody-targeted therapeutic constructs may very well be derived from that kind of research?

(*Professor Anderson*) Yes. The trouble with bacteria is that they are not a single entity and they are constantly evolving and changing.

(*Dr Bax*) The last truly novel antibiotic which was produced was nalidixic acid in 1962 and vancomycin in 1959. Since then everything has been molecular roulette on existing agents. The pharmaceutical industry has been very successful up to now in keeping just ahead of the bacteria. We are failing now particularly in hospitals but also, very importantly, in the community. The antibody and host immunity approach to infection is not new. Sir Almroth Wright was head of the department of chemotherapy and microbiology at St Mary's when Fleming discovered penicillin. He was mentioned in George Bernard Shaw's *The Doctor's Dilemma* in relation to stimulating the phagocytes. These are not new. With molecular biology and new techniques we are finding out many different ways in which we can potentially attack bacteria, for example sensing agents whereby bacteria communicate and turn on and turn off different virulence factors. To say that the pharmaceutical industry is likely to produce new agents in the next few years is very much an overstatement. I believe that the harvest from our bacterial genome activities with academia and ourselves and in co-operation with other companies is only just a start. We first identify targets and then need to produce agents which must be as safe and effective as penicillin. This means that we must use our existing products very much more effectively to maintain or reduce the gap between developing resistance and increasing morbidity of infections. That is where the focus lies. Companies like mine and many others and a lot of academics have numerous antimicrobial targets. It remains to be seen whether they will be

viable. If a new antimicrobial agent came out it would be highly restricted by definition. It may be that the pharmaceutical industry on the basis of those restrictions decided that new antibiotic agents were not of major commercial interest. However, the FDA and some other regulatory authorities had a meeting in April of last year in which they said they would fast-track, in a regulatory sense, novel antimicrobials with a narrow spectrum of action. To date no company has progressed that.

(*Dr Stephenson*) The genome projects are producing many exciting things. Some fundamentally new concepts are only just beginning to emerge. The ideas to which you have referred have been around for many years. What is particularly exciting about the genome projects which we do not get from any other type of research is that by knowing the total genetic activity or information in the bacteria we know not only what it has but what it does not have. This has produced some novel insights into the way in which bacteria live and survive in their environments. These projects also provide information about control elements. We can now target the control elements in whole pathways of important bacterial proteins and so provide truly novel targets for vaccines and drugs. This is cumulative not just for one bacterium but for all of them. There are already many exciting new insights. But as Richard Bax has said, to transfer those from the laboratory into the pharmaceutical industry is a much longer pathway.

Lord Dixon-Smith

693. In studying the genome for a bacterium you produce a wonderful amount of information. Presumably, you study a consistent sample of a bacterium. It seems to me that one of the great problems of bacterial resistance is that there must be within a particular species of bacterium a very rare factor of genetic variation. Unless you manage to identify what causes that genetic variation in your study of the genome you will have a problem. To do that you will probably have to study hundreds of millions of individual ones. Is that right?

(*Professor Anderson*) You are spot on. In a sense, there is a great deal of excitement in the scientific community about sequencing the genome of mycobacterium tuberculosis, but your point is totally relevant. The Wellcome Trust has already thought about what the future holds in funding here. I am sure that applies also to the Medical Research Council. We now need to think about setting up genetic diversity studies in which we repetitively sample many bacteria from many patients and carry out molecular epidemiological surveillance internationally. The cost and scale of such approaches will be very high given current technology. But that technology has evolved very rapidly in the past year. There are now DNA chips for particular parts of specific genomes which may be the antigenic diversity bit, or the resistance bit, from which we can develop quick and accurate sampling methodologies. One can lay a specific genome against the chip to see its differences and similarities. I believe that in the next five years once

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[Continued]

[Lord Dixon-Smith *Contd*]

most of the major bacterial genomes have emerged—rumour has it that there are a very large number already sequenced by the pharmaceutical industry, and it is sad that they are not in the public domain—the focus will change to diversity. This is important not only for antibiotic resistance but for vaccine development. There is only one major pathogenic organism that has been repetitively sequenced at the whole genome level at present: HIV. That is a virus with a small genome. There is a repetitive sequencing centre in the United States and the current database runs to about 150 whole genome sequences. When one understands that one individual AIDS patients has 10^{11} viral particles one realises that sampling at present is just scraping the surface. People always regard astronomy as a big science in terms of the scale and measurement of variables. By comparison biology is emerging as a very big science in terms of the measurement and description of genetic diversity.

Lord Phillips of Ellesmere

694. It is one thing to know the genome sequence but it is a further problem to know the function and nature of the gene products. Is there any hold-up in interpreting what the genes are doing?

(*Professor Anderson*) I expect that most of our grant applications and those of the MRC in this area will be very much related to trying to sort out the function of a new gene. For example, the Lyme disease bacterium was sequenced and that was published in *Science* just before Christmas. A lot of that genome was totally novel. They are new genes and we do not know what they do. I suspect and hope that research organisations will be deluged with grant applications to explore the functions of those genes. That is optimistic but it depends on having the qualified scientists who can take advantage of the new whole genome information.

695. Even though there have been advances in this area, it remains true that to characterise the gene products, namely the proteins, is a much more slow and more difficult process than simply sequencing the gene?

(*Professor Anderson*) That is where the pharmaceutical industry has a great advantage over the university science base because it requires large interdisciplinary teams comprising, for example, protein chemists, crystallographers, molecular biologists and so on all targeted on that particular function. Most academics' mouths water when they walk round the industry's laboratories at present—given the poor state of research laboratories and equipment in many British universities.

(*Dr Bax*) SmithKline Beecham has an agent that is a tRNA synthetase inhibitor which inhibits protein production in cells. Two years ago we knew of two of these. Through the human genome project and protein expression we have now identified 17. Within two years we have 17 totally new targets. The aim is to produce compounds that inhibit several of these which will produce a broad spectrum of protection and higher

potency. That is a good example of the pharmaceutical industry's involvement in protein expression.

Baroness Masham of Ilton

696. Do you think that information and surveillance is accurate enough? Can it be improved?

(*Professor Anderson*) You would get the same response internationally. The microbiological community would like to have vastly improved surveillance, carefully designed sampling for individual patients and carefully designed sampling of the community. At the moment, the Public Health Laboratory Service responds to samples received, not in a carefully structured sampling framework. We need a great deal more information, but it is costly to acquire and priorities must be set.

Lord Jenkin of Roding

697. Dr Bax and Professor Anderson recognised that there were limits to what the pharmaceutical industry could be expected to do in this regard. At the end of Dr Stephenson's evidence there is a very short paragraph about the orphan drug initiative. We have heard a good deal about that from other witnesses who feel that there is a considerable corpus of knowledge which can be exploited if the means are found to do it. One cannot expect the pharmaceutical industry, which must have regard to the bottom line, to pick that up. Can you explain a little more what you are doing?

(*Dr Stephenson*) This is quite a complex issue and so there has not been a tremendous amount of extra activity since I wrote that note. To recap, there was an initial proposal by the Wellcome Trust to establish a consortium of companies, governmental organisations and non-governmental organisations to set up a not-for-profit company to develop orphan drugs, i.e. drugs which the pharmaceutical industry will not target because they are not profitable for one reason or another. This particular initiative had very strong support from the World Bank and the WHO and was designed primarily to look at diseases in tropical countries which the Trust and many other organisations target as being of importance. Of course, the prime concerns would be malaria and tuberculosis. Late last year there was a meeting of the chief executive officers of the major drug companies and several complex issues in this area were identified. The main issue was that there was already some activity in this area on the part of many pharmaceutical companies. Therefore, the International Federation of Pharmaceutical Manufacturers was given the job of undertaking a survey of current research and development in pharmaceutical companies in this area. That is the situation at the moment.

698. By definition, if the pharmaceutical companies are willing to take certain initiatives they cease to be orphan drugs. One is looking for the ones where it has been decided that for one reason or another research cannot be taken forward. It seems to me that this is an area where a body like Wellcome can come in and help.

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[Continued]

[Lord Jenkin of Roding *Contd*]

(*Professor Anderson*) The Wellcome Trust feels that its major areas are not in bacteriological fields. Looking at the international needs for orphan products and take the world's leading infectious disease killers, we believe that our efforts should be targeted towards drugs and vaccines for malaria and dengue vaccines, other viruses that are very problematic at present and a variety of other areas where we are looking at parasitic infections as opposed to bacterial ones. That will be our first priority. However, if a bacterial disease which was unique to the tropical world came up—and there are one or two—where scientific research suggested avenues for the development of a product we would be very keen to try to help.

Baroness Platt of Writtle

699. The educational initiatives which you described as raising the public profile are evidently concerned mainly with professionals. On page 1 of your paper you list some great experts in a tremendous number of fields. On page 2 you say: "Uninformed drug prescribing practices by GPs and demands from their patients may be linked to an increase in drug-resistant bacteria". We have received similar evidence from others. I thought that your *Wellcome News* article was very interesting and touched on the same question. Obviously, it would be of use to qualified people. But do you have any initiatives aimed at the wider public, medical and non-medical?

(*Professor Anderson*) Your point about prescribing practices is an extremely interesting area. In a sense, there has been a recent significant change in the recording of data in general practice. Something like 90 per cent of general practices now use GP database computerised systems. It is very rare for a research person to purchase that data for the subscription is very costly per year: but in collaboration with the pharmaceutical industry it has been possible for some academics to get access to these databases. One then poses the question: is there enormous heterogeneity in treating a particular condition—a sore throat, pharyngitis, whatever? Analyses of these quantitative databases reveal extraordinary heterogeneity. There may be best practice information available. It appears that a good deal of information needs to be targeted at the professionals in the health sector. I rather hope that these electronic and digitised databases can be a way of pushing forward this process. General practitioners are all doing things differently. Why?

(*Dr Stephenson*) The Trust, responding to an initiative from Henry Wellcome himself, has always been very interested in the general public understanding of science. The Wellcome Trust Centre has a lot of activities in this area. To give a flavour of what we do, since 1991 we have run educational programmes targeted at the general public, particularly teachers in primary and secondary schools. Since 1993 the Trust has opened a Science for Life exhibition at its centre in Euston Road. It has a number of other exhibitions. Those with the highest profile at the moment address the interface between science and art. We have a road show called *Genes Are Us*. We have

also commissioned a couple of plays about depression and genetic diseases. We run lab workshops for A level students on DNA extraction and genetic engineering. We encourage school visits to the Trust building to look at the exhibitions there and we organise workshops in the Trust building. Those visits are vastly oversubscribed; the waiting lists extend to several years. We also run training programmes for teachers which we believe are particularly important for science teachers in secondary and primary schools. Very few primary teachers have formal scientific training. Other activities include a "People's Parliament" which was a programme on television which looked at human genetics. In the last five years a £3 million investment in this area has been made. We have also awarded over £3 million in grants on public understanding of science activities. Last year the governors decided to refocus the activities with the public and in future direct activities into supporting and facilitating public debates on ethical issues, a theme echoed by the Office of Science and Technology. We work very closely with several ethical committees which have a significant government impact. Over the next few years we expect our investment in this area to top £6.5 million. In addition, we have made major contributions to the new wing of the Science Museum and other activities through the Lottery Millennium Fund. We take the public understanding of science very seriously, because that is where the future lies. Hopefully, it will help to address a lot of the problems that you are facing today.

700. As a former member of the Royal Society's Committee on the Public Understanding of Science, I believe deeply in the importance of this subject. Obviously, you deal with it on a very broad basis, thinking of teachers and school children. You will understand that we have received a great deal of evidence, including some from the developing world where often antibiotics are sold over the counter. We are told that the world is a global village and bacteria are extremely clever and travel very quickly in terms of resistance. It strikes me that if children have antibiotics prescribed to them it will probably be the mothers who press for them, even though the doctor may not believe they are desirable. It may be that in the developing world they have bought them and they are valuable, but then they see the cure starting and stop taking them. It seems to me that the education of mothers in this matter is very important and may be done simply through publicising some of the work that you are doing in women's magazines, for example?

(*Dr Stephenson*) That is a very interesting idea, and I shall pass it on to people in charge of this area. I should like to take this opportunity to deal with another issue: education in the tropics. The Trust has had a long-standing interest in research in the tropics and tropical medicine. Over the past years we have established something called the Tropical Medicine Resource. It is a series of CD-ROMs designed to educate young doctors, health workers, students and the educated layman in the tropics. It is very user-friendly and addresses all of these issues. CD-ROM technology is now available to many people

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[Continued]

[Baroness Platt of Writtle *Contd*]

throughout the developing world. By that means we seek to educate those people who would then pass on their education to the mothers whom you quite rightly identify as the people to be targeted.

Lord Porter of Luddenham

701. Dr Stephenson, you will be familiar with the Committee on the Public Understanding of Science (COPUS). Do you feel that what COPUS is doing is enough? Quite a lot of money from government, the Royal Society, the British Association and so forth goes into it. From your face, it appears that you have some comments to make on how it may be improved?

(*Dr Stephenson*) I do not think that I have any specific suggestions to make. Everyone supports the work of COPUS very strongly. More and more members of the scientific community are beginning to recognise that it is important for them to make understandable to the general public what they are doing. That will counteract a lot of the future problems and the bad publicity that science has had in the past.

702. Since COPUS has been in existence it has become respectable for professional scientists to dabble in these matters.

(*Dr Stephenson*) Yes. But there can never be enough. There are always more imaginative things to do. One of the exciting matters that the Trust is exploring—perhaps COPUS should explore it further—is the need to spend more time in schools, particularly primary schools. I have always been amazed at the development of my children. Just about all school children are fascinated by science, especially biological science, until the age of 11 or 12. There is an enormous body of interest and support there which should be developed further.

703. At our meetings we have talked a good deal about the difficulties that doctors experience with the public. When they say, "You do not have a bacterial infection and you should not have an antibiotic", they are stamped on and it is very difficult to say "no". Do you see any way of educating the public to understand the doctor's problem?

(*Dr Stephenson*) I was very interested in Baroness Platt's idea of targeting everyday women's and men's magazines. That is probably a very good way of getting this kind of information to the general public.

Lord Gregson

704. The specific problem of pneumococcal resistance throughout the world is a matter of great concern. Should it be approached by new vaccines or drugs or both? What procedures can be applied?

(*Professor Anderson*) On the scientific side it would be nice to see both approaches pursued vigorously. Clearly, there are some interesting products in this area coming through which will enter vaccine trials. Before one goes vigorously to trials it is important to understand the genetic diversity of these organisms in particular communities so that you know what the vaccine which is targeted against one subset will do to the remaining subsets of strains. There has

been only one country-wide experiment worldwide with a view to trying to reduce resistance in pneumococci. That was carried out in Iceland which had an extraordinarily well developed database. Over a period of about 12 years very high levels of resistance emerged rapidly. The government carried out an experiment in which they reduced the volume of penicillin use and monitored the change in the frequency of resistance. It is the only quantitative experiment worldwide of this nature. The encouraging result from it was that it proved possible to lower resistance levels by reducing specific drugs' use and using others as substitutes. Undoubtedly, the pharmaceutical industry and research and academic communities will pursue both lines of research—vaccines and new drugs.

(*Dr Bax*) Professor Anderson knows what I am about to say because it is a tack and line on which I have been very keen. I should like the Sub-Committee to consider three factors in a triangle, as it were. Resistance is at the top. At the bottom are antibiotic use and outcome as the two legs of the triangle. If you connect them you get questions which are fundamentally different and explain a lot of the confusion. There is the effect of antibiotic use on resistance and outcomes. I suggest that the reason why GPs and patients have problems in deciding when to give antibiotics is that the effect of antibiotics on outcomes has been incompletely researched and understood. I am very keen that the effect of resistance on outcomes is fully understood and is of key importance in managing the whole problem. In the Icelandic situation the incidence of penicillin resistant streptococci and pneumococci in the nasopharynx of children attending day care rose to approximately 22 per cent. With a significant reduction in antibiotic use, which was instituted through the fact that the Icelandic Government reduced the amount of reimbursement of antibiotics, it went down to 17 per cent—a very small decrease. However, those resistance determinants are still in the Icelandic population. Under the influence of antibiotics the microbiology changes, but the resistance determinants are still there for ever. My contention is that it is very important to look at the effects of the resistant organisms and what happens to patients. Both Professor Anderson and I are in contact with the Icelandic Government and Icelandic microbiologists to see whether the impact of infection, cost of infection and hospitalisation over that period has increased or decreased. It is people's opinion that it has increased. The overall morbidity and mortality have increased. However, we must show it. We can show it if we have databases linking prescribing with appropriate microbiological epidemiology and the effect of antibiotics on resistance. We need to have databases which are patient-oriented and express good outcomes which are reasonable and reliable. Once we get all three we can begin to dissect out the value of antibiotics to individual patients. Until we do that we are not able to manage the problem.

705. I have seen it suggested that the interrelationship between children and elderly people is a particularly dangerous one, because most of the

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[Continued]

[Lord Gregson Contd]

resistance is caused by over-prescribing to young children, and the effect on old people can be disastrous.

(Professor Anderson) The quality of epidemiological research in this area is limited. Recently, there was a meeting at Oxford to try to put together a group of people who put a proposal to the Department of Health and a number of other funding agencies to set up a long-term study of pneumococcal resistance. It requires choosing a birth cohort and repetitively sampling them throughout their lives into adulthood. That is the approach of the non-infectious disease people who study such things as cancer, heart disease, birth weight and so on. That will not solve our policy-making problem in the short term, but there is a desperate need for better quality information based on the accurate monitoring of bacterial infection experience from birth to death. There is much opinion as to what determines observed epidemiological patterns, but when you go to the research papers it is very difficult robustly to defend any one hypothesis about the determinants of observed diversity and age-related acquisition rates.

Baroness McFarlane of Llandaff

706. You have spoken about how you focus some of your research and choose priorities, but we have heard that the Wellcome Trust's interests in this area of research have a bias towards pathogenesis and immunity. The problems of antimicrobial resistance do not seem necessarily to conform comfortably with that approach. Do you recognise this description and do you believe that there should be a change?

(Professor Anderson) That is very fair comment. It is quite easy to tease through the titles of the research grants that have been funded. Certain words are fashionable at certain times. "Pathogenesis", "virulence factors" and "immunology" in relation to bacterial infections are fashionable words. Grant applicants are not unaware of fashions. Even though the detail of the research project may be a little removed from that area they often include those words. We say robustly that we are responsive to the community; we respond to its requests. Our initiatives have been in the field of molecular genetics and genomes. We are spending an increasing fraction of our money on the understanding of the genetic diversity of these organisms. We spend a bit on epidemiology at the moment, but I suspect that that fraction will increase. Therefore, our interests are much, much broader, but we depend on the community coming to us to say, "Would you be interested in funding this sort of research?"

Lord Rea

707. How far can a research charity such as Wellcome sway the overall pattern of applicants who seek support?

(Professor Anderson) Very easily, as Lord Phillips will know! If an initiative is announced in a particular field for the purposes of applications for research grants, whether it be related to interdisciplinary

research centres or whatever, typically the community responds quite quickly.

708. That gives you a fairly onerous responsibility; in other words, you have power to steer a particular branch of research?

(Professor Anderson) That is correct. But how is policy made here? I hope that the scientific and medical communities feel that The Wellcome Trust spends an enormous amount of time sampling their opinions. They are the ones who sit on panels and assess grant applications and make contributions to policy formulation of the Trust. I argue that we sample their opinions and try to do things differently from government but based on guidance from the research community.

709. I do not suggest that your decisions are bad but that they can have a major influence.

(Dr Stephenson) Another important aspect of the Trust's activities is its attempts to strengthen the link between the laboratory and clinic. In this area we have quite substantial schemes so that young clinicians can be trained in fundamental research. We feel it is very important that there is a cadre of clinically trained people who are really up to date with what goes on in the research lab and are able to discuss and formulate ideas so that exciting discoveries made in the molecular genetics laboratory can be applied as rapidly as possible to the clinical situation.

Lord Porter of Luddenham

710. It has been represented to us quite strongly that there is an important funding gap in research between fundamental and applied. We are told that it is difficult to do non-fundamental work in the universities and the NHS because of their constraints and that fundamental work because of its nature is not funded by the pharmaceutical industry and yet is considered as of low priority by the major funding bodies. Examples of this include applied microbiology in hospital infection, clinical trials and so on. Are you aware of this problem? Do you have any idea as to how the gap could be filled?

(Dr Stephenson) We are very much aware of the problem. At the moment, it is the Trust's policy to fund fundamental research. We are acutely aware of the problems of clinical research and have recently started an initiative to establish new clinical research centres associated with a number of British university laboratories. We believe that what goes on in hospital, how the hospital manages itself and determines best practice is more appropriate for the Department of Health or the hospital trust itself.

(Professor Anderson) This is related very much to the quality of the applications. Unfortunately, in some areas the quality has not been sufficient to satisfy the review panels. Review panels tend to be populated by the brightest and best at basic research. Perhaps we should alter the structure to choose a few more individuals who are very much in applied areas.

711. When you answered an earlier question related to this matter you said that in this field there

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[Continued]

[Lord Porter of Luddenham *Contd*]

were not many requests from the community. Do you mean that the requests you receive are perhaps not of the right quality?

(*Professor Anderson*) It is both. There are few requests and those that come in often do not get past the review panels because of quality.

Baroness Masham of Ilton

712. I should just like to ask about clinical research workers. Given the great pressure in hospitals, do they all have time to do what they want to do?

(*Dr Stephenson*) They would say no. We are very much aware of this. Certainly, the recent schemes that the Trust has initiated are always done in close consultation and collaboration with the relevant Royal College. We ensure that at least one member of the Royal College sits on the interviewing committee as part of the process to ensure that these people are given genuine protected research time and their clinical careers are not derailed by this.

Lord Dixon-Smith

713. You mentioned your research fellowships in medical microbiology. How many are there and what sort of work are they doing? Are those who hold the fellowships able to find work subsequently more easily or less easily than might otherwise be the case? Do they find that having done the research they are in a cul-de-sac, or are they enhancing their career prospects by doing this?

(*Dr Stephenson*) So far over the past four years during which the scheme has been operating we have appointed nine people to this fellowship. It is a little lower than we would like, but the feedback from the community is that it is making a considerable difference. As to those who have been appointed so far, it is too early to give you a definite answer because these are five-year fellowships and they have been running for only four years. Already one has been appointed as head of the PHLS's new TB research lab, which is also a reference lab, and another, Dr Pallen, headed up the successful University Challenge team from Imperial College last year. I do not know whether that is a measure of success! The subjects are very broad: the genetics of HIV infection, the pathology of HTLV, which is an important virus causing Leukaemia in children, the pathogenicity of salmonella and TB itself, the pathogenicity of streptococcus and a variety of other subjects. We get the impression—we will know for certain next year—that it is greatly enhancing their career prospects by having defined research time in very good quality research labs in this country and abroad.

714. You said that the number of fellowships awarded at the moment was perhaps fewer than you hoped. Does that take us back to the question of the quality of the application, or are there rigorous hoops that you make people jump through before they are accepted?

(*Professor Anderson*) There are a number of factors relevant to the question. I have been chairing

this particular fellowship interview committee for the past four years. With any new scheme it takes a little time to get the information into the community for it to develop, so we expect to underspend the money allocated in the first few years. The underspend has been quite significant. We could probably have funded double the number of fellowships on the money allocated to the project. The reasons why that is so are two fold. First, the question related to whether the clinically qualified physician has enough technical expertise to put together a quality research application. Often the answer is no. Secondly, many of them wish to stay in the institute where they are—it may be a medical school in London, Oxford, Cambridge or Edinburgh—where the basic scientific expertise to give them new technologies and skills in microbiology may not be of the best available worldwide. We find that we have had to encourage a very significant fraction of the successful applicants to spend a period of time particularly in the United States at very high quality laboratories to gain new techniques and skills. The second reason is that in medical microbiology we have tried to tackle it from the point of view of both the clinician who wishes to acquire scientific skills and the high quality scientist who wants to work in a medical environment. There is some distinction here in the career prospects between the medically qualified and the scientifically qualified. Although in many medical departments things have changed recently, in the recent past the very high quality scientist would have been at a disadvantage in the promotional and salary stakes within the medical schools. Recently, because of the difficulties of filling some very important medical microbiology chairs in the United Kingdom a number of medical schools have lent more towards appointing a scientist with appropriate remuneration who has responsibilities for inserting new skills into the medical community. Hopefully, in future we will be able to train more of both and there will be less discrimination in either direction.

Lord Phillips of Ellesmere

715. Is there a Catch-22 here, in that the non-medical microbiologist believes that he will not make it to the top in the medical aspects of the subject and the medically qualified microbiologist feels that to spend too much time on research is an interruption in his career path to the top of that profession?

(*Professor Anderson*) Absolutely right.

Baroness Masham of Ilton

716. Overall, there is a shortage of doctors in this country. Does that have anything to do with it? Have quite a few of our high quality people gone abroad?

(*Professor Anderson*) I cannot give a factual answer to that. Impressions are always dangerous in this area. In some of the very basic areas of biomedical research the very best are attracted by top laboratories in the States. However, it is equally true that a number of senior appointments in the United Kingdom recently

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[Continued

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have been filled by Americans. I cannot quantitatively give you an answer.

Chairman

717. We have received a good deal of conflicting evidence on the role of animal use and its relationship to human health. The funding of veterinary research into antimicrobial resistance is very limited. You also hinted at the quality of the applications that come forward. Have you any plans to enhance this in any way?

(*Professor Anderson*) It is a very difficult area, especially as I am giving evidence before you, my Lord Chairman, with your expertise and knowledge in this field. Five years ago the director of the Trust, Dame Bridget Ogilvie, was very keen to mount a veterinary research initiative and the Wellcome Trust might have put in £10 million plus per annum if the opportunity had arisen. Information was spread throughout the veterinary schools in the United Kingdom. The responses were extremely disappointing in terms of new initiatives, ideas and opportunities to give veterinarily qualified young people time to do quality research and acquire quality training in specialised environments. We were so frustrated by the lack of co-ordinated response that the scheme was put in abeyance by the governors because they saw better

ways of spending money in the absence of any high quality requests from the veterinary community. Just recently the issue has re-emerged. All of us in the Trust would like to spend money in the field of veterinary research. There are some glimmers of particular universities making the investment in quality people to put applications to the Trust. For example, the University of Edinburgh has recently invested money in some chairs. We hope that we may receive major applications from them. In the veterinary microbiology area the situation is a little desperate. In my period of time on the infection and immunity panel of the Wellcome Trust (the past five years) I have very rarely seen an application in this area. Those that have come in by and large fail, with a few notable exceptions.

Lord Walton of Detchant] My Lord Chairman, perhaps I may ask a question that is better directed at yourself! I was informed by an officer of the Wellcome Trust that one of the problems was that within several veterinary schools there was opposition on the part of students to scientific research because they felt that the money should be better spent on animal welfare. Is that a problem with which you are familiar?

Chairman] It has been said but it is not a major problem at present. It has certainly arisen in one veterinary school. Gentlemen, thank you for coming along.

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Memorandum by Dr G C Schild *et al*, National Institute for Biological Standards and Control

VACCINES AND THE CONTROL OF INFECTIOUS DISEASE

INTRODUCTION

Our ability to protect against infectious diseases by vaccination stems from the pioneering work of Edward Jenner on smallpox over 200 years ago and Louis Pasteur's work on rabies some 100 years ago. Since these early beginnings, enormous progress has been made in reducing the burden of infectious diseases in both the developed and developing countries of the world by well organised vaccination programmes, which have emphasised the protection of children in particular. During the latter half of the present century, the impact of several common infectious diseases has been dramatically reduced, and child survival rates have been improved remarkably in many countries, largely in many cases, as a direct result of vaccination. The effect of vaccination in reducing the impact of infectious disease in the UK and in the USA are illustrated in Tables 1(a) and 1(b) respectively which show the decline of vaccine-preventable diseases in various time periods up to 1996.

Using well established, safe and effective vaccines, the WHO Global Programme on Vaccines focuses international efforts on immunisation against eight major diseases: diphtheria, tetanus, pertussis, tuberculosis, measles, poliomyelitis, yellow fever and hepatitis B.

Even more impressive is the possibility of eradication of previously prevalent diseases by vaccination. It is a remarkable achievement that smallpox has been totally eradicated by vaccination, the world's last known case having occurred in 1977. This was made possible by the use of an inexpensive and effective vaccine and by intensive international co-operation. Another great achievement is that large areas of the world are now free of poliomyelitis as a result of massive international vaccination efforts, and the WHO target of eradicating polio by early next century seems achievable. The global incidence of measles has also been dramatically reduced by vaccination programmes, and in several countries with highly vaccine uptake rates, such as the UK, measles is now a rare disease. Future targets for global immunisation are *Haemophilus influenzae* group b (Hib), (a major cause of infant meningitis and pneumonia) and rotavirus (a major cause of infant diarrhoeal disease). Attention is also being focused on introducing new vaccines against meningococci and pneumococci which cause meningitis, septicaemia and respiratory disease.

Vaccination has thus made enormous contributions to public health and is a highly cost effective intervention. An analysis of cost benefit factors has led the World Bank¹ to conclude that vaccination against the eight WHO target diseases is the most cost effective intervention in public health that any government could provide for its population, the estimated cost of vaccines required to provide basic life-long immunisation being some \$3–5 per child in 1993 for basic vaccines supplied through UNICEF programmes.

Unlike the situation for antibiotics, the effectiveness of widespread vaccination does not, so far, appear to have been hampered by the emergence of vaccine-resistant strains of bacteria or viruses. For example, vaccines against polio and measles designed in the 1950s and 1960s are still as effective as they ever were, despite some 30 or more years of extensive international use.

Historically, the development of vaccines was based on empiricism and the application of basic biological principles. The traditional methods of vaccine design and development, that is the use of inactivated (non-infectious) bacterial or viral antigens or the use of living attenuated (non-pathogenic) organisms, continue to serve us well. However, the past 15 years or so have seen major scientific and technical advances relevant to vaccine design and production which could provide the basis for a quantum leap in progress in vaccination. There are now prospects for extending vaccination to diseases for which no vaccines of proven efficacy are currently available. New science and technology will also add to our ability to improve the effectiveness, safety and affordability of existing vaccines. The new approaches arise from advances in gene technology, biotechnology, molecular biology and an improved knowledge of the immune mechanisms involved in vaccine-induced protection. Radically new principles of vaccine design, such as that of nucleic acid vaccination (see below) are now the subject of intensive research internationally and offer great promise in the long term.

As we near the end of the 20th century much has been achieved by vaccination and there are excellent prospects for the future. Several major international initiatives—such as the WHO Global Programme on Vaccines and Immunisation (GPV) and the International, multi-agency Children's Vaccination Initiative (CVI)—provide organisational and political impetus as well as the basis for intensive international co-operation and are a catalyst for progress.

Recent history has shown that new infectious disease threats to mankind continue to occur (for example HIV—AIDS, Ebola and pandemic influenza) and these present new and complex challenges for vaccination. Although historically, vaccination has emphasised the control of acute infectious disease, new scientific approaches lead to possibilities for its application to the prevention and treatment of other types of disease, such as cancer.

¹ World Bank, 1993, World Development Report: Investing in Health, Washington D.C., USA

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We now have enormous technical and scientific potential to extend vaccination to the great benefit of public health but harnessing the new technology will require sustained research and development activities. There are areas where serious deficiencies in basic scientific knowledge (e.g., in some aspects of immunology, microbial genetics, epidemiology and pathogenesis) are limiting the rate of progress in extending and improving the control of infectious disease by vaccination.

This paper summarises the status of vaccination against bacterial and viral infection, but deals with the former in greater detail, since it is essentially in the case of bacterial infections where drug resistance is already a major public health problem. However, viral resistance to antiviral drugs is also a potential problem. Vaccination has great potential to control some of the infections for which the effectiveness of anti-microbial approaches are being progressively eroded by drug resistance. A major future challenge for vaccinology will be to control infections for which antibiotics have diminished effectiveness.

VACCINES AGAINST BACTERIAL INFECTIONS

Vaccination has proved highly successful in preventing several important bacterial infections. Thus diphtheria, tetanus, pertussis and Hib are almost non-existent in populations immunized routinely with good quality, specific vaccines. Vaccines are also available for use in appropriate circumstances for the prevention of anthrax, botulism, cholera, meningococcal disease, pneumococcal disease, tuberculosis and typhoid fever. The examples cited indicate that the emphasis in vaccine development has been concentrated on serious, acute infections. Less success has been achieved in developing vaccines against the bacterial causes of infections which do not have such a high profile but may actually be more common and cause a large burden of morbidity. Many of these are caused by bacteria frequently carried by healthy individuals as part of their normal flora. The development of vaccines against such organisms has not been pursued as vigorously as it could have been because the introduction of antibiotics reduced the urgency for a preventive approach. In addition some infections, e.g., gonorrhoea, streptococcal and staphylococcal infections, have proved refractory to the vaccine approach. Nevertheless, the increasing emergence of antibiotic organisms has raised the need for renewed development efforts.

The infections in which resistance to therapeutic agents has emerged as a significant problem fall into four main categories:

- community-acquired infections
- hospital-acquired infections
- opportunistic infections
- exotic infections

Vaccines are currently available for prevention of some of these infections (Table 2) but for the majority effective preparations do not yet exist. However, vaccine development is either proceeding or would be feasible for many others (Table 3).

1. VACCINES AGAINST COMMUNITY-ACQUIRED INFECTIONS

(a) *Tuberculosis*

Drug-resistant *Mycobacterium tuberculosis* is an increasing problem world-wide. Multi-drug resistant (MDR) disease in which the bacteria are resistant to two or more drugs is very difficult and expensive to treat. Although new therapeutic agents are under development, resistance to these may also emerge in time. It is widely accepted that the only practicable approach to this problem is prevention by vaccination. The currently available BCG vaccine, although effective in preventing tuberculous meningitis in children, has produced conflicting results against more common forms of the disease in efficacy studies done under different conditions and there is a consensus that a more effective preparation is needed. The most promising approaches to the development of new tuberculosis vaccines include:

- (a) nucleic acid vaccines which consist of specific DNA molecules¹
- (b) purified mycobacterial proteins (e.g., secreted in cultures of bacteria or prepared by recombinant technology), delivered with a suitable adjuvant; and
- (c) genetically modified mycobacteria for use as "designer" live vaccines.

Hitherto, none of these have been assessed in clinical trials and efficacy still has to be determined. In view of the increasing impact of tuberculosis globally, in associated with HIV and AIDS, the need for ongoing research in this area is paramount.

¹ Nucleic acid vaccines consist of a small molecule of DNA of bacterial origin called a plasmid which contain a gene encoding a foreign antigen. Expression of the foreign gene is controlled by a eukaryotic/mammalian regulatory sequence. After inoculation into a vaccinee, the foreign gene is expressed and the product of that gene stimulates the individual's immune system inducing both antibodies and T-lymphocyte responses.

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(b) *Pneumococcal infections*

These are a major cause of morbidity and mortality at all age levels but particularly at the extremes of life. Otitis media is one of the commonest infections of young children and the cause of enormous morbidity. Its management has considerable cost to the community. Pneumococcal meningitis, pneumonia and septicaemia are life-threatening infections which affect all age groups. They are difficult to treat and even when caused by antibiotic-sensitive strains are associated with substantial mortality. Otitis media results in an enormous burden of hearing disability. Penicillin resistance is now common and resistance to alternatives such as macrolides and tetracyclines is increasing. Vaccines based on capsular polysaccharides alone will induce protection in older individuals but are not effective in infants. This is because they do not stimulate certain types of T-lymphocytes associated with long-term protection. Conjugates of the polysaccharides with carrier proteins (referred to below as glycoconjugates) are immunogenic in infants and are currently undergoing clinical trials in the UK and elsewhere. This strategy has previously proven highly effective for *Haemophilus influenzae* (Hib) vaccines. If successful, the present research will lead to introduction of pneumococcal vaccines into routine immunization schedules. However the large number of capsular serotypes (>80, with about 30 commonly causing disease) makes the conjugate approach difficult. There are also hints of serotype variation in response to vaccination. Vaccines based on antigens common to all or most types of pneumococci would be preferable. Research on surface and released proteins suggests that this may be feasible.

The existence of extensive antigenic heterogeneity is a general problem for certain groups of organisms for which vaccination might be desirable, e.g., in addition to pneumococcus and several other groups of bacteria, it also applies to certain viruses such as the common cold virus (> 100 serotypes), HIV and influenza. One of the challenges is to attempt to identify common, well conserved antigenic components which could be used as vaccines, giving broad protection.

(c) *Meningococcal infections*

Meningococcal infection is a major cause of death and disability, including serious intellectual and hearing impairment, in children under five. It also has a high profile as a cause of sudden devastating infection in young adults. In the UK about one third of cases are caused by serogroup C and nearly two-thirds by serogroup B. Meningococci of serogroup A, a major cause of epidemics in Africa and occasionally elsewhere, account for less than 1 per cent of UK cases. Serogroups W135 and Y also account for a minor proportion of infections. Penicillin resistance is slowly emerging and resistance to cephalosporins and quinolones can be anticipated. Polysaccharide vaccines are available against serogroups A, C, W135 and Y. Like the pneumococcal polysaccharide vaccines these do not stimulate effective responses in the very young and so are of limited efficacy and application. More effective glycoconjugate vaccines against serogroups A and C have been developed and are under evaluation in Department of Health-sponsored clinical trials in the UK, the results of which are very encouraging. These vaccines are likely to be introduced into immunisation schedules as soon as they are licensed.

The situation is much less satisfactory for serogroup B, the commonest type. The serogroup B polysaccharide is poorly immunogenic in humans and cross-reacts antigenically with nerve cell-adhesion molecules and other tissue components and so raises concerns about possible adverse autoimmune reacting due to responses. The conjugate approach will probably not be applicable. Attention has been directed towards developmental vaccines based on bacterial surface proteins rather than polysaccharide, which have been developed in Cuba, Holland and Norway. These vesicle vaccines have achieved some success in older persons but not in infants. Attention has been directed towards other proteins, especially those whose expression is regulated by environmental factors, such as available iron concentration. However, these like the other outer membrane proteins vary between strains. They are only likely to confer broad protection as a "cocktail" of different types. No clear solution is in sight and research in this area needs to be promoted.

(d) *Gonorrhoea*

Resistance to antibiotics commonly used for treatment is frequently observed. Chromosomal resistance and plasmid-mediated resistance to penicillin is now widespread. The occurrence of quinolone resistance is a serious emerging problem and will make single dose oral therapy increasingly difficult, with serious implications for disease control. A considerable research effort has been expended on vaccine development, mainly focused on pili¹ and outer membrane proteins. This has yet to produce an effective product although some clinical trials are still in progress. The genetic variability of the organism and its elaborate immuno-evasion processes mean that an effective vaccine will be elusive. Nevertheless, this may offer the only long-term prospect for controlling the disease.

¹ Pili are surface projections on certain bacteria, the functions of which include adhesion to surfaces, motility and transfer of DNA. They are abundant on meningococci and gonococci

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(e) *Haemophilus* infections

H. influenzae type b infections are currently well-controlled by vaccination with the glycoconjugate vaccines. The possibility of an increase in prevalence of other serotypes exists and needs to be monitored. Vaccines are not available for these haemophili and antibiotic resistance is making management increasingly difficult. The development of non type-specific vaccines would be very desirable. Various outer membrane proteins are being assessed as the basis of subunit vaccines, particularly for the prevention of diseases caused by non-typable haemophili, of which otitis media and lower respiratory tract infections (chronic bronchitis) are probably the most important.

H. ducreyi, the cause of chancroid—a genital ulcer disease, is frequently antibiotic resistant. Although uncommon in the UK, it is imported from Africa and Asia where it is an important co-factor for HIV acquisition. Vaccine development is at a very early stage and the mechanisms of pathogenesis and immunology of the disease are poorly understood.

(f) *Enteric* infections

Gastro-intestinal infections caused by *Salmonella* and *Campylobacter* serotypes are among the commonest reported bacterial diseases in the UK. Most infections result from food contamination from animal sources. Antibiotic therapy is not usually indicated or encouraged except in severe cases. Antibiotic resistance is fairly frequent and probably increasing. The diversity of serotypes makes vaccine development and implementation very difficult. More research is needed to assess the feasibility of this.

Pathogenic *Escherichia coli* infections are a common cause of enteric infection and worldwide may account for more cases of acute diarrhoea than any other agent. Cytotoxic strains, especially 0157, have emerged as a cause of severe disease. A vaccination strategy may be possible for these and research on vaccine development is being pursued.

Shigella infections are fairly well-contained in the UK but common in Third World countries. Antibiotic resistance is frequent. Vaccines of both live attenuated and glycoconjugate type are undergoing clinical trials.

Typhoid fever is uncommon in the UK and most cases are imported. Resistance to chloramphenicol and ampicillin is common in endemic areas. Resistance to ciprofloxacin, the drug of choice, is likely to become more frequent. Several vaccines (Ty 21a live attenuated vaccine, Vi polysaccharide vaccine and a killed whole-cell vaccine) are available but give limited protection. Improved live attenuated vaccines have been developed but are not yet licensed.

(g) *Helicobacter pylori*

This bacterium was discovered only in 1983, but it is an important pathogen of man, colonising the gastro-intestinal tract. It is a major cause of morbidity and mortality from gastritis, gastric and duodenal ulcers and gastric carcinoma and lymphoma. Therapy with a cocktail of antibiotics controls or eliminates the infection and is widely used in the treatment of ulcers. However, resistance to antibiotics is frequent and relapse or reinfection can occur. Vaccines are under development but vaccine design is complicated by the genetic variability of the organism and resistance to vaccination may be a potential problem. Because of its enormous public health importance, research relevant to vaccination against *Helicobacter* should be encouraged and supported.

(h) *Urinary tract* infections

These are a common cause of morbidity. Most infections are caused by gram negative bacteria, particularly *E. coli*. Although uropathogenic strains of the latter have been implicated in a proportion of infections, a variety of serotypes are involved and the development of an effective vaccination strategy would be difficult.

2. HOSPITAL-ACQUIRED INFECTIONS

Staphylococcus aureus, *Bacteroides*, *Burkholderia*, *Pseudomonas*, *Stenotrophomonas*, *Streptococcus*, *Proteus*, *Enterococcus*, *Klebsiella* and *Acinetobacter* are common causes of nosocomial infections in patients with wounds, burns and other debilitating conditions. These organisms are frequently resistant to multiple antibiotics and infections can be very difficult to treat. They are usually harmless to healthy individuals but can cause life-threatening disease in surgical, burns or immunocompromised patients. Methicillin resistant *S. aureus* (MRSA) has achieved most notoriety and will become an increasing problem now that strains resistant to vancomycin and teicoplanin have emerged.

Vaccines have been developed for prevention of *Klebsiella* and *Pseudomonas* infections in burns patients but are not widely applied. Time constraints usually make their application post-injury impracticable.

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Patients with in-dwelling catheters are at particular risk of developing infections with coagulase-negative staphylococci and MRSA, among others. Vaccines against these organisms could be useful in selected patients.

Limited development of vaccines against the other common nosocomial pathogens has been attempted. The difficulty of identifying at-risk individuals will make implementation difficult. Universal vaccination would be likely to be prohibitively expensive and of doubtful value. *Clostridium difficile* causes toxic enteritis in patients treated with broad spectrum antibiotics; institutional outbreaks also occur. Vaccines based on detoxified toxin proteins are under development.

3. OPPORTUNISTIC INFECTIONS

These can be divided into infections occurring in otherwise healthy persons and those developing in the immunologically or physiologically compromised. A major problem in healthy women is vaginal candidiasis. Various drugs are available for treatment, including azoles and flucytosine but resistant strains of *Candida albicans* are becoming increasingly common. There is no reason to believe that effective vaccines could not be developed against this organism and experimental data are encouraging.

Fungal and bacterial infections are a serious problem in immunosuppressed and severely diabetic patients. Unfortunately, because the problem arises from loss of immune function in the patient, vaccination seems unlikely to offer solutions.

4. EXOTIC INFECTIONS

Drug-resistant infections that are exclusively acquired abroad include malaria, leishmaniasis and melioidosis. Multiply drug-resistant *Yersinia pestis* has been reported recently and is a potentially serious problem, although importations of plague are very rare. More common enteric infections caused by *Campylobacter*, *E. coli*, *Salmonella*, *Shigella* may be acquired abroad or in the UK. These are frequently resistant to a range of antibiotics.

Malaria is one of the major causes of mortality and morbidity worldwide and drug resistance of the parasite itself is of great concern as is insecticide resistance of the vector mosquitos. Resistance of the parasite to chloroquine is common and in many areas resistance to alternatives such as mefloquine, proguanil and artemisin has also emerged. Malaria is now quite frequently imported into the UK and often presents problems in diagnosis and treatment. Vaccine development is a very high priority and some promising progress has been made. Synthetic peptide vaccines have proved inconsistent in clinical trials but nucleic acid vaccines and recombinant proteins with suitable adjuvants appear more promising. This field is a high priority for research.

RESISTANCE TO BACTERIAL VACCINES

There is no general and unequivocal evidence to suggest that widespread vaccination with bacterial vaccines encourages the selection of vaccine resistant strains. Although recent reports from Holland have claimed that micro-variation in some *Bordetella pertussis* genes has resulted in the emergence of vaccine escape mutants, this has not yet been independently confirmed but merits urgent study. Studies in South Africa and Finland have also indicated a shift in pneumococcal serotype prevalence following use of conjugate vaccines. The possibility of emergence of vaccine resistance needs to be borne in mind and surveillance programmes are needed to monitor this.

VACCINES AGAINST VIRUS DISEASES

Antiviral agents and Viral Vaccines

Antiviral agents are not common because of the nature of the interaction between the virus and its host. Viruses are essentially intracellular parasites using the same machinery as that of the host cell to replicate. It is therefore difficult to design non-toxic anti-viral drugs and successful anti-viral treatments are rare. They have, however, included treatment of herpes infections with nucleoside analogues and more recently the use of protease and polymerase inhibitors for the treatment of HIV. Strains of HIV rapidly develop resistance to individual inhibitors, and the molecular basis of resistance is well understood. It is possible that current intensive international research work on HIV drugs will herald a new era in the chemotherapy of viral infections in general. However, so far the best general method for controlling viral infections has been to prevent them by the use of vaccines. The problems of resistance to anti-microbial agents are likely to arise with antiviral compounds where these are used extensively.

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Prophylactic viral vaccines

As for bacterial vaccines the development of the viral vaccines in current use has been based on two basic principles, the use of inactivated (non-replicating) viral antigens and live attenuated organisms. Many of the vaccines in current use (see Table 4) are live attenuated viral strains which mimic the natural infection in an asymptomatic form.

The list of successful prophylactic vaccines is extensive. It includes vaccines against small pox, yellow fever, poliomyelitis, mumps, measles, rubella, varicella, hepatitis A, Hepatitis B, and rabies. Some have been in use for over a 100 years, such as the killed vaccine against rabies, while the live yellow fever vaccine has been in use for over 50 years. With the sole exception of hepatitis B vaccine, which consists of a viral protein expressed by recombinant DNA technology, all vaccines in current use were developed by traditional methods, either involving the identification of attenuated strains on passage, or the use of killed virus or viral proteins. This approach has proved highly effective for over 200 years and is still applicable. While the use of materials of poorly controlled potency can lead to inadequate protection, which could at least in theory be exploited by variant viruses, there is no evidence for the emergence of strains of virus able to escape immunity induced by any of the current successful vaccines used correctly.

The specific problem of influenza has received attention recently as a result of the possible emergence in Hong Kong in 1997, of a new, potential pandemic strain of the virus previously only found in birds and designated influenza A (H5N1). Influenza is able to infect a wide range of hosts (man, horses, swine and birds) and the biggest reservoir of infections is believed to be avian. The genome is composed of eight separate segments and the infection of a suitable host with two strains can lead to reshuffling of the genomes to generate reassortant viruses which can change their host range, so that a virus of chickens could theoretically adapt rapidly to infect humans. The generation of a new virus to which the human population has not previously been exposed can then result in a global epidemic or pandemic, assuming that the other properties of the virus relating to transmission are appropriate. The emergence of a new virus in this way is termed "antigenic shift". However, influenza strains are also able to vary by the gradual accumulation of point mutations, giving less drastically different viruses which are associated with more restricted, but almost annual, epidemics. The generation of epidemic strains by this route is termed "antigenic drift". The variability of the influenza virus has caused problems in developing and assessing vaccines. Indeed, because of the uniquely high degree of antigenic variability of the influenza virus the composition of the vaccines must be revised annually. The vaccines typically contain three different influenza viruses representative of currently prevalent strains. The vaccine viruses must be a close antigenic fit for currently prevalent strains in order to protect adequately. To monitor the emergence of new viruses the WHO maintains a network of some 90 National Influenza Centres situated in most major countries of the world which carry out intensive surveillance of influenza epidemics, referring new viruses to the International Centres in London and Atlanta for detailed analysis.

Antiviral agents against influenza have been sought, the most successful of which so far are amantidine and rimantidine. They have been used in epidemics in both human and veterinary settings. While the drugs have value, e.g., in controlling outbreaks in residential communities and the management of high risk patients, the virus is rapidly able to develop resistance. Influenza virus therefore poses a particular difficulty with respect to both vaccines and antiviral agents.

Vaccines may not give full protection against some enteric infections, such as those caused by rotaviruses. However, even where protection is only partial, vaccination is nevertheless effective in the broader context of preventing serious disease and death. Rotavirus vaccines, for example, may give complete protection against enteric disease requiring hospital treatment, while not preventing infection.

The development of an effective vaccine against hepatitis B, a major cause of serious liver disease and liver cancer, is a case worthy of special comment and is an important milestone as the first successful vaccine to be developed by modern recombinant technology. The hepatitis B virus cannot yet be cultivated and therefore traditional approaches to vaccine design were not possible. The earliest hepatitis B vaccine was based on hepatitis B purified from the serum of carriers. Current vaccines are prepared in large amounts in yeast cells by recombinant DNA technology and so far are the only extensively used vaccine to be prepared to modern biotechnology. The vaccine is being used as part of a WHO programme to control hepatitis B and reduce the incidence of the hepatitis B carrier state, which is very high in some countries, and ultimately to prevent hepatocellular carcinoma associated with chronic hepatitis B infection.

Other vaccines which could potentially protect against cancer would be directed against papilloma and Epstein Barr viruses. Such vaccines are under clinical evaluation.

It is clear that vaccines to uncommon infections are unlikely to be developed as the effort involved is difficult to justify commercially. Vaccine-induced protection is generally organism specific, not broad as is the case with certain classes of antibiotic.

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HIV AND AIDS

The emergence and rapid spread of AIDS in the 1980s and 1990s has proved a hard challenge for modern medicine. The failure of infected individuals to eliminate the infectious agent, HIV, even in the presence of an immune response is unlike the behaviour of most other types of virus and suggests that vaccination may be problematic. A successful vaccine will have to induce a protection not normally observed in natural infection. A number of drugs to combat AIDS are now available and improvements in their use, e.g. as in combination therapy with three drugs, have been able to slow the progress of disease in infected individuals. However, it is unlikely that current drugs will be able to bring about a complete cure. Compliance with a heavy dosing regime of expensive drugs is required and for every drug developed so far drug resistant virus variants have been identified and they appear readily in patients. The most likely means to control AIDS in the world is through the development of an effective vaccine. Many imaginative approaches are being used in research and development work on HIV vaccines and information on the type of immunity needed to protect is far from complete. The goal of vaccine development is hampered by the considerable genetic variation observed between HIV isolated from different parts of the world. At least seven genetically distinct varieties (clades) of HIV exist (see Table 5). Nevertheless progress has been made and clinical trials are underway in the US, UK and Europe using vaccines based on components of the virus envelope, molecularly engineered so it may be produced safely in large quantities. Even if this type of vaccine proved to be successful in the developed world, we will need to determine whether changes will be required to make the vaccine suitable for use in other areas of HIV prevalence, e.g., Africa, Asia or Latin America. Novel vaccine strategies have been identified through basic research. These are being developed and may provide us with the broadly protective AIDS vaccines, which we urgently require.

THERAPEUTIC VACCINES

Most antiviral vaccines in use are exclusively prophylactic, rather than therapeutic, as once an individual is infected giving antigenic material in addition to the amount being made by the infection is unlikely to speed up the immune response. However, there are a few examples where vaccines are used effectively after exposure to modify the course of infection. The notable example is rabies where post-exposure vaccination (e.g., following a rabid dog bite) is strongly recommended and effective. Even where the vaccine can be successfully given post exposure, as for rabies, the success of the procedure depends on the slow progression of the virus to the target organ, giving time for protection to be induced before symptoms develop. Similarly, there is hope that eventually vaccines against hepatitis B will be developed that are able to eliminate established chronic infections by inducing the correct immune responses but they are not available yet in any convincing form. Recent attempts to treat patients with multiple drug resistant TB, by the use of a proposed therapeutic mycobacterial vaccine were, unfortunately, not successful. Attempts are also being made to develop therapeutic vaccines for *Helicobacter* infections.

Therapeutic vaccines against cancer are under study, and aim to induce immune responses to tumour specific antigens which may be viral in origin as in the case of papilloma virus induced cervical cancer. BCG (tuberculosis) vaccine is used, with some success, as a non-specific immunostimulant for the therapy of bladder cancer.

NEW APPROACHES TO VACCINE DEVELOPMENT AND RESEARCH NEEDS

The development of vaccines to cover disease problems not previously dealt with by vaccination will probably require the application of new strategies, as well as building on the experience gained from well tried conventional approaches. The application of the traditional approaches to vaccine design, such as the use of inactivated bacterial or virus vaccines or empirically attenuated strains, may meet with only limited success for certain pathogens and we will need to exploit the novel approaches which are not becoming available. New approaches include novel vaccine design strategies and vaccine presentation systems.

Among promising new vaccine design strategies are those employing bacterial glycoconjugates or protein-protein conjugates (to modulate responses to poorly immunogenic materials). Nucleic acid vaccines, containing cloned DNA sequences, purified viral or bacterial subunits prepared by controlled gene expression or the use of genetically modified organisms, e.g., with precise attenuating mutations as live vaccines, all offer hope for valuable applications.

The way that vaccines are formulated for use is important for their effectiveness. New adjuvants will be required to enhance and target specific types of immune response, to minimise reactogenicity and to maximize protective efficacy. New developments in formulation will also be needed to simplify immunization schedules and to target more convenient routes of immunization, e.g., by oral or respiratory routes. WHO is co-ordinating international development work on new "single dose" delivery systems for vaccines which work by enabling the slow release of the antigen over several months after injection. These have the potential to induce protective immunity following a single dose of vaccine, rather than the two or three doses normally required and offer promise of simplifying and reducing the cost of vaccination programmes.

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The issue of potential microbial resistance to vaccination needs to be addressed. To monitor this possibility adequately, research on viral and bacterial variability, immune selection and the maintenance of epidemiological surveillance will be required in order to monitor this possibility adequately.

If the new biotechnology is to be harnessed to maximum effect in vaccination there is a continuing need for research and development work in several key scientific areas. Studies of mechanisms of immunity to infection to identify those aspects relevant to specific diseases and vaccination will be continuing importance. The role of T cell helper subsets in determining the direction of the immune response (TH1 or TH2) needs to be defined for individual infections. In the case of infections entering through mucosal surfaces the specific cell interactions and effector mechanisms of protection will need to be defined. Investigations of organism-specific mechanisms of pathogenesis will also be needed for new vaccine targets. This is particularly the case for organisms which are part of the normal flora but have potential to produce disease following increased susceptibility of the host e.g., following surgical or medical intervention.

In the UK the need for an increased initiative on vaccine development has led to the recent formation of the Jenner Institute to promote interaction between government, the research councils and industry.

REGULATORY ASPECTS FOR VACCINES

An essential part of the process of bringing a new vaccine to market and into general use involves dealing with the regulatory hurdles, including clinical evaluation, licensing, quality control and standardization.

For vaccines, as for all complex biological substances used in medicine, the application of carefully chosen, scientifically based and rigorously applied regulatory approaches to ensure the safety, efficacy, quality and consistency is of crucial importance. The quality of vaccines is of paramount importance to public health and has implications above and beyond those for the vaccine recipient particularly where vaccines comprise live, potentially transmissible agents. Quality assessment of vaccines requires the application of specific and complex biological assays and a specialized cadre of scientists. Vaccines are unusual in that international requirements specify that each batch should be independently tested by a National Control Authority before release for marketing. New products, such as, for example, nucleic acid vaccines, will require new regulatory approaches and standards which, in turn, require applied research work for their development.

The UK National Biological Standards Board has recently commissioned an international group of independent experts under the Chairmanship of Sir Leslie Turnberg, Past-President of the Royal College of Physicians, to carry out an in-depth Scientific Review of Biological Standardization and Control. The Report of the group includes comments on current approaches to the standardization and control of vaccines and future challenges; it has been published by the World Health Organization.¹

CONCLUSIONS

Vaccination has proved highly successful and cost-effective in controlling several major diseases caused by bacteria and viruses. Because of early successes in and the widespread use of, antimicrobial therapy, vaccination has been less actively pursued for the prevention of diseases amenable to treatment with antibiotics. However, with the emergence of antimicrobial resistance as an increasing problem, vaccination merits further evaluation as an approach to the control of a much wider range of diseases particularly where drug resistance is a major problem. Vaccine development and vaccination are, in the long run, likely to prove more cost-effective than new therapeutic agents, which are increasingly expensive to develop and license.

Powerful new technologies are now available for vaccine development. However, each infectious agent has to be approached as a separate entity and new vaccines will have to be developed on a case-by-case basis. A substantial input into research and development will be required if vaccination is to realise its full potential in controlling infections that are not amenable to antimicrobial therapy.

It is likely that the next decade will see the development of several new vaccines, including vaccines against diseases where antibiotic resistance is problematic. Vaccines of improved effectiveness against meningitis, including types of which there are currently no effective products, and against pneumococcus are expected in the short term. In the longer term vaccines against malaria and improved tuberculosis vaccines are likely. Progress will be made in the clinical evaluation of developmental HIV vaccines.

It should be recognised that the lead time between identifying a new vaccine target and the licensure and use of the final product is long (e.g., 10–30 years) even when new technologies are employed. Consequently it is important that we attempt to anticipate future needs for vaccines, as far as is possible, and to maintain a suitable level of scientific research in appropriate disciplines and adequate resources for development and clinical evaluation. Both the public and private sectors have a role in this objective, hopefully in close collaboration and in an international context.

¹ Biological Standardization and Control—A Scientific Review Commissioned by the UK National Biological Standards Board, WHO, Geneva 1997–9 WHO/BLG/97.1). See also N. Morris, Biological regulation—Biological medicines in the age of biotechnology: public policy issues in Science and Public Policy, volume 24, number 1, February 1997, pages 53–61.

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TABLE 1(A)

Reduction in the Incidence of Various Vaccine-preventable Diseases in England and Wales

Disease	Before vaccination		After vaccine use ²	
	number of cases ¹	baseline year	notifications	lab reports
Diphtheria	46,281	1940	12 ³	
Measles	409,521	1940	5,614	63
Mumps	20,713	1989	1,814	48
Pertussis	53,607	1940	2,390	326
Polio	1,066	1940	0	0
Rubella	24,570	1989	9,253	1,295
Congenital Rubella Syndrome	73	1971		1
Tetanus	19	1969		8
Haemophilus influenza type b	655	1989		49

¹ Notifications except CRS and Hib.² 1996 except 1995 for CRS and Hib.³ Includes some non-toxicogenic cases.

TABLE 1 (B)

Reduction in the incidence of various vaccine-preventable diseases in the United States (1921–1993)

Disease	Before vaccination	After vaccine use
Diphtheria	206,939 ¹	1921 ² 2 ³
Measles	894,134	1941 676
Mumps	152,209	1968 1,663
Pertussis	265,269	1934 6,146
Polio (wild)	21,269	1952 0
Rubella	57,686	1969 188
Congenital Rubella Syndrome	>20,000	1964–65 7
Tetanus	601	1948 45
Haemophilus influenza type b	20,000	1984 1,282

¹ Number of reported cases of disease in the USA in the year indicated.² Baseline year.³ Cases in 1993.

TABLE 2

Vaccine availability and efficacy for common bacterial infections

Disease	Antimicrobial Resistance	Vaccine Types	Efficacy
Cholera	Increasing ¹	Killed whole cell Live attenuated	Low, short term
Diphtheria	Uncommon ¹	Toxoid	>90 per cent
Haemophilus influenzae b infection	Common	Polysaccharide-protein conjugates	>90 per cent
Lyme disease	Uncommon	Outer surface protein	Immunogenic in clinical trials
Meningococcal infection	Increasing	ACW ₁₃₅ Y polysaccharide A and C conjugates Group B outer membrane vesicle	Variable, short term, not suitable for infants In clinical trials ~57 per cent short term in clinical trials
Pertussis	Uncommon	Killed whole cell acellular	up to 95 per cent 70–85 per cent
Pneumococcal infection	Common	23-valent polysaccharide multi-valent polysaccharide-protein conjugates	Variable, not suitable for infants In clinical trials
Tetanus	Uncommon ¹	Toxoid	>90 per cent
Tuberculosis	Common	BCG (live attenuated)	Variable (0–75 per cent)

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Disease	Antimicrobial Resistance	Vaccine Types	Efficacy
Typhoid	Common	Killed whole cell Vi polysaccharide Ty 21 a live attenuated Aro-mutants, live attenuated	up to 70 per cent up to 70 per cent Variable In clinical trials

¹ Antimicrobial therapy plays a minor role in management.

TABLE 3
Prospects for developing vaccines against major infections

Disease	Antimicrobial Resistance	Prospective Vaccines	Comments
Campylobacter enteris	Common	In early stages	Numerous serotypes
<i>Chlamydia trachomatis</i> genitourinary infection	Uncommon	OMP vaccines under development	Main cause of sexually transmitted disease in UK
Chancroid	Common	In early stages	Uncommon in UK
<i>E.coli</i> (ETEC)	Common	Adhesin + toxin B subunit	Numerous serotypes
<i>E.coli</i> O157	Common	In early stages	Verocytotoxin a potential target
<i>E.coli</i> (uropathogenic)	Common	Adhesin	Numerous serotypes
Gonorrhoea	Common	OMP and pili	Little success in clinical studies
<i>Klebsiella</i> burn and wound infections	Common	Polysaccharide—protein conjugate	Under evaluation
Malaria	Common	Synthetic peptides, rDNA and DNA	Limited success. DNA vaccines promising
<i>Salmonella enteritidis</i> enteritis	Common	Live attenuated and conjugate	Numerous serotypes
Shigella dysentery	Common	Live attenuated and conjugate	In clinical trials
<i>Staphylococcus aureus</i>	Common	Protein and cell wall component	In early stages
<i>Staphylococcus epidermidis</i>	Common	In early stages	
<i>Streptococcus pyogenes</i>	Uncommon	M protein derivatives	In early stages
<i>Streptococcus agalactiae</i>	Uncommon	Polysaccharide conjugate	For neonatal infections
Tuberculosis	Common	Live attenuated strains, secreted proteins DNA vaccines	At pre-clinical stages

TABLE 4
Vaccines against viral disease of humans

Vaccine	Type	Developer and date
Small pox	Live pox virus	Jenner 1795
Rabies	Killed virus	Pasteur 1885
Yellow fever	Live attenuated	Theiler 1945
Influenza	Killed, viral protein	1943
Polio	Killed	Salk 1954
	Live attenuated	Sabin 1960
Measles	Live attenuated	1968
Rubella	Live attenuated	1970
Mumps	Live attenuated	1966–86
Varicella	Live attenuated	1974
Hepatitis B	Plasma antigen	1982
Hepatitis B	Recombinant	1986
Hepatitis A	Killed	1998?
Rotavirus	Live attenuated	1946
Tick Borne Encephalitis	Killed	1954
Japanese B Encephalitis	Killed	1999?
Dengue	Live attenuated	

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TABLE 5

International Distribution and Frequency of HIV Genetic Variants (Clades)

Clade	A		West and East Africa, Russia
	B		Europe, North and South America, Australasia, South East Asia
	C		East and South Africa, India, China, Brazil
	D		East Africa
	E		South East Asia, Central Africa
	F		South America, Central Africa
	G		East and West Africa
Clade	A	=	23 per cent of HIV isolates worldwide
	B	=	16 per cent of HIV isolates worldwide
	C	=	36 per cent of HIV isolates worldwide
	D	=	13 per cent of HIV isolates worldwide
	E	=	7 per cent of HIV isolates worldwide
	Others	=	5 per cent of HIV isolates worldwide

M J Corbel, P D Minor, D Salisbury (Department of Health) and G C Schild

National Institute for Biological Standards and Control

Examination of witnesses

DR GEOFFREY SCHILD, Director, DR PHILIP MINOR, Head, Division of Virology, and DR MICHAEL CORBEL, Head, Division of Bacteriology, National Institute for Biological Standards and Control (NIBSC), were called in and examined.

Chairman

718. Gentlemen, thank you for attending this morning.

(*Dr Schild*) My Lord Chairman, I am the director of the National Institute for Biological Standards and Control. The Institute is a non-departmental public body dedicated to securing high standards of quality, safety and efficacy for biological substances used in medicine, including vaccines.

(*Dr Minor*) My name is Dr Philip Minor, head of the Division of Virology at the Institute.

(*Dr Corbel*) I am Dr Michael Corbel, head of the Division of Bacteriology at the same Institute.

719. Do you have any opening comments to make?

(*Dr Schild*) We emphasise in our written submission the immense contribution that vaccines have made and continue to make to public health in both developed and developing countries. They have transformed the burden of infectious disease and remarkably improved child survival. They have the potential to eradicate previously prevalent diseases and they are highly cost-effective. Over the past 10 years there have been remarkable advances in science and technology, some of which we heard in the previous evidence session, including gene sequence information for bacteria and viruses, molecular biology, improvements in understanding immune mechanisms and the availability of excellent tools such as monoclonal antibodies. These create the potential for further developments in vaccination and perhaps the development of vaccines against diseases for which there is none at present, more affordable vaccines or vaccines of increased effectiveness where the present

vaccines are of limited efficacy. I am sure that vaccines will be able to contribute to the solution of problems arising as a result of microbial resistance to antibiotics.

The United Kingdom is in an excellent position to take an international lead in vaccine development. We have in position a co-ordinated vaccine evaluation group which involves key institutions in the United Kingdom working closely with the Department of Health. The group involves the PHLS, NIBSC and CAMR who closely integrate their activities and are evaluating some new vaccines at the moment. I believe that this interdisciplinary approach is very important. There are also other new initiatives in the United Kingdom including the foundation of the Jenner Institute. The MRC/BBSRC and Department of Health have been working on a strategic plan for vaccines. We, at NIBSC, work very closely with other laboratories in the European Union, and indeed, have been successful in securing valuable EU grants that enable us to collaborate.

720. The first question is about the lead time in vaccine development. Of particular concern to us are meningococcal and pneumococcal infections. Can you give any idea of the likely lead time in that area and in relation to malaria and tuberculosis, which I understand you would place in the longer term?

(*Dr Schild*) There is a lot to do between identifying an organism and having a licensed, well tried vaccine. History has shown us that for a relatively simple virus like polio it took at least 15 years to develop a safe and effective vaccine. It is now some 15 years since the first identification of the causative agent of HIV. We know an enormous amount about

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DR GEOFFREY SCHILD and DR PHILIP MINOR

[Continued]

[Chairman Contd]

the agent itself but we still have no effective design for a vaccine. There are however a number of candidate vaccines under investigation. We are very near to achieving improvements in vaccination against meningitis and pneumococcus. Perhaps Dr Corbel can tell us about that. A recent survey in industry showed that even when you know a lot about a particular organism and you have identified the target it may take nine years to carry out all the necessary clinical studies leading up to licensing.

(Dr Corbel) To give some more specific information on meningococcal vaccine, the problems breaks down into two parts. Infection in the United Kingdom is caused mainly by sero- groups B and C. Sero- group B causes about two-thirds of cases and sero- group C about one third, with other groups like A and W135Y causing a very small proportion of infections. The news in relation to the group C vaccines is good, in that polysaccharide-protein conjugate vaccines constructed on similar principles to those used for the very successful *Haemophilus* vaccines have been in clinical trials for some time and have shown very good immunogenicity results in infants, which is the main target group. On the basis of the information accumulated, manufacturers are now prepared to submit licence applications which will probably go in towards the end of this year. This means that we can anticipate the group C conjugates being available for use by the year 2000. If experience with the Hib vaccines is anything to go by, it is very likely that this will deal very effectively with meningococcal infections caused by sero- group C. This is a slightly more complex problem because there is a much wider age range involved. Nevertheless, there are grounds for quite considerable optimism. The situation in relation to group B vaccines is much more complex. The conjugate approach is not really viable because the group B polysaccharide is very poorly antigenic. Although you could prepare a conjugate there are potential hazards in doing it, in that the material cross-reacts with normal tissue, so there is considerable anxiety about going down that route, even if it proved to be an effective approach to improving the immunogenicity of the antigen. The alternative approach is to use various protein antigens, including the outer membrane proteins on the surface of the organism. The problem with that is that they undergo considerable strain variation. For example, horizontal genetic transfer occurs in meningococci and the process of antigenic variation can take place very rapidly. One gets antigenic shift and drift, much in the same way as one gets it in influenza viruses. To formulate a vaccine out of protein components is quite difficult. Nevertheless, there are some that are currently manufactured in certain countries, for example Cuba and Norway. There is an experimental vaccine in Holland. Clinical trial results have shown that these give some degree of protection in older individuals but not in infants. It is possible that the formulation of these vaccines can be improved by incorporating other proteins such as iron regulated proteins. Those are also variable and a cocktail approach would have to be taken. If that were done it is unlikely that a vaccine of this type would be

available for general use in less than five to 10 years, taking into account the need to accumulate clinical data. One would have to accept that the vaccine would not be wholly effective because of the range of serotypes that occurs in the United Kingdom and the fact that they are subject to constant change.

721. What about the microbiology of tuberculosis?

(Dr Corbel) The situation in relation to tuberculosis is quite complex. The BCG vaccine has been around for about 70 years. It has very variable efficacy according to different studies in different countries. It is widely accepted that it does not give very satisfactory protection against adult forms of the disease. The search for vaccines has been focused on the development of genetically modified live attenuated strains and on formulations which include secreted proteins from live bacillus tubercule bacilli and, more recently, genomic vaccines based on cloned DNA sequences from *Mycobacterium tuberculosis*. On the basis of laboratory studies so far, most promising are the DNA vaccines but even they have not given results better than the BCG vaccines in experimental systems. So far no products have yet gone to clinical trials. Because of the nature of these in relation to the chronic nature of the disease and its sporadic incidence it will take a long time to accumulate efficacy data on new products. I believe it is highly unlikely that there will be new candidates for a tuberculosis vaccine in less than 10 to 15 years.

722. We heard earlier about the sequencing of the genome. Will it speed it up or will it go along at its previous pace?

(Dr Corbel) I believe that it will help considerably because it will identify target sequences which could be incorporated into DNA vaccines. I believe that it will be of considerable benefit.

Baroness Masham of Ilton

723. If we are a long way from the production of a new vaccine for tuberculosis do you think that we should be pushing for better facilities to look after sufferers?

(Dr Corbel) I do not have any information on that but I would have thought that as a matter of principle it would be a good idea. Drug resistance, although very worrying, is not a huge problem in the United Kingdom at the moment.

724. It is becoming a problem in HIV and AIDS sufferers who are particularly susceptible to it?

(Dr Corbel) That is certainly true.

Lord Walton of Detchant

725. Now that the genome of the *Mycobacterium tuberculosis* has been elucidated, is it known whether certain segments of the DNA produce the intrinsic bacterial protein and others produce, as it were, the bacterial coat or membrane? If that is the case, is there a risk that in searching for DNA vaccines a single point mutation or deletion may affect the antigenicity of any vaccine?

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[Continued]

[Lord Walton of Detchant *Contd*]

(*Dr Corbel*) That is a potential problem. We have no idea what the optimum protective antigens are in tuberculosis. There are certain proteins, such as secreted proteins, that have been identified as protective antigens, but none of those in experimental studies has produced very good protection. Possibly it can be improved by better adjuvant formulations.

726. Do you see any bottlenecks, financial or otherwise, in the development process of vaccines, and do you believe that at the moment there are adequate administrative and financial resources for funding vaccine trials?

(*Dr Corbel*) That is a fairly large question. Are you thinking specifically of tuberculosis or generally?

727. Generally.

(*Dr Corbel*) Generally, there are a number of bottlenecks to which one can draw attention. In the public sector probably one of the major problems is the translation of laboratory research into industrial high quality material suitable for use in clinical trials. Clearly, there are limitations in that area. The private sector is probably better set up for it.

(*Dr Schild*) I said in my introductory remarks that in the United Kingdom, NIBSC, PHLS, CAMR had organised themselves into a Vaccine Evaluation Group, the work of which is co-ordinated and funded by the Department of Health. I should also emphasise the importance of working closely with industry. We have a very comfortable way of working with industry which does not create conflicts of interest where the contributions from the public sector complement the activities and contributions of the private sector. I am sure that that sort of interaction accelerates the process of bringing an idea to fruition in terms of a licensed vaccine. There are very many examples of that, including the examples that Dr Corbel mentioned in relation to meningococcus and pneumococcus.

Lord Phillips of Ellesmere

728. When the AIDS crisis emerged in an acute form Dr Schild will remember very well that the MRC launched the AIDS directed programme which brought about collaboration between fundamental research workers and industry. I know that Dr Schild played an important part in that. Do you see any of these problems as being usefully approached by the same method?

(*Dr Schild*) I was privileged to be the director of the MRC AIDS Directed Programme which had two objectives: to develop a vaccine and to develop novel anti HIV drugs, and to co-ordinate enabling research. We worked very closely with industry. We brought about the involvement of the academic scientific community. Very many longstanding collaborations evolved. The work on vaccines is still going on even though the Directed Programme came to a natural end in 1994. There are vaccines being evaluated clinically now which saw the light of day in the programme that I managed. I think that the Programme had a lasting impact and accelerated progress. Would the strategy of having a directed programme be applicable, valuable and politically acceptable for any of the other

infectious disease problems? I have an open mind. I believe that it had substantial advantages in getting research to move very rapidly and involving all aspects of the scientific community, including industry. Because of the enthusiasm generated by a Directed Programme it might have attracted overmuch emphasis to a particular problem and thereby reduced efforts in other fields. It is not for me to say. However, I believe that it was a useful initiative at the time.

(*Dr Minor*) I think it is worthwhile making a distinction between different types of vaccine trials. One can have a fairly small scale vaccine trial brewed up by a biotech company or academic institute. The sort of thing I have in mind is therapeutic vaccination against carcinoma of the cervix where some limited trials are going on at the moment with perhaps 10 people being involved. You can contrast that with a large-scale paediatric vaccine trial where you are looking at the efficacy of a particular vaccine. For the first kind of trial, which may be of particular interest, the process can be extremely daunting. Dr Corbel has already mentioned the question of producing material under appropriate conditions for clinical use, which would not be a problem in a large scale commercial trial. There are also regulatory hurdles which are very daunting, if you happen to come from an academic background. It seems to me that at least potentially there might be greater co-ordination between the various regulatory agencies, which rightly have an interest in the safety of the trials, to make the small scale trial simpler than it is at the moment.

Baroness Platt of Writtle

729. Your paper indicates that vaccine prospects are poor for most hospital acquired infections. Are there any infections of this type for which extra research effort is likely to be fruitful?

(*Dr Corbel*) This is a very complex area. Hospital acquired infections encompass infections caused by a very large range of organisms. Most of these are either commensal organisms on the skin or mucous surfaces or in the intestine or they are environmental bacteria. The main problems are caused by *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Enterococcus* and so on. I will not give you a complete shopping list. There are a large number of organisms which have a remarkable ability to acquire antibiotic resistance.

730. The patients are weaker anyway?

(*Dr Corbel*) That is the other problem. The patients affected usually have some predisposing condition or have had surgical interventions that breach natural barriers. Another difficulty is targeting particular patients for vaccination. Clearly, it is not practicable to vaccinate everyone against every commensal or environmental organism that they may come across. But there are certain organisms that would probably be worth targeting because they are a frequent cause of infection and are a particular problem in relation to microbial resistance. *Staphylococcus* is one of them; another is *Streptococcus*. The others would be very difficult to

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[Continued

[Baroness Platt of Writtle *Contd*]

target in a practical manner, although some work has been done on *Pseudomonas* and *Klebsiella* vaccines particularly for burns patients and other special category patients.

731. Are patients vaccinated now?

(*Dr Corbel*) No. These have been experimental vaccines. One of the problems with acute patients is that you do not have time to vaccinate them. I think that if you are to use vaccines in this situation you will probably have to target them against patients with chronic disease or those going for elective surgery where you have the time to raise an immune response.

Lord Rea

732. Can you tell us about the possibility of future "therapeutic" vaccination after infection in other slowly developing diseases with a long incubation period, such as rabies? Would that kind of approach be suitable for HIV and other infections, or is it even in the running for this?

(*Dr Schild*) There are major biological differences between rabies infection and HIV in the sense that the latter produces at a very early stage a generalised infection. There is a viraemia and infection is spread to many organs of the body. The characteristic feature of retroviruses, a family to which HIV belongs, is that it is an RNA virus but a DNA copy of the genome is produced, which is capable of integrating into the genetic material of the host cell. Having integrated, it can provide a template for the generation of new virus. The characteristic features of HIV make it extremely difficult to envisage eradicating the infection once initiated. You would almost have to destroy the chromosomes of the host cells to do so. Experimental studies on HIV models to examine the possibility of a therapeutic vaccine have been made and the results do not look promising.

Chairman

733. Some of the considerations here relate to active vaccination. Is there a role for passive applications—anti-sera, anti-toxins?

(*Dr Schild*) Studies have been made using immunoglobulin from HIV infected subjects given therapeutically patients. This was done in the United States. This approach received quite a lot of attention some years ago. I suspect that the results have not been very encouraging.

734. I was thinking not so much of HIV but hospital infections like *Staphylococcus*.

(*Dr Corbel*) This approach has not been widely explored recently. There has been some interest in using antibody preparations against bacterial endo-toxin. Unfortunately, these have not given very successful results but the approach probably deserves further examination.

(*Dr Minor*) My point has to do with the therapeutic vaccines. There are no therapeutic vaccines in the strict sense. Once the infection is established it is too late. But in the context of something like HIV I suspect that the disease or its transmission could be

moderated by vaccinating individuals so that one suppressed certain populations of virus with respect to others.

Lord Rea

735. After transmission?

(*Dr Minor*) To prevent individuals transmitting or to reduce the transmissibility of viruses. In a sense it would be an altruistic vaccine which would be very good for controlling AIDS but probably not much good for the individual patient.

Lord Walton of Detchant

736. The other point about passive immunisation is that the serum itself is seriously antigenic. The complications that arose with diphtheria antitoxin and for tetanus antiserum were substantial and in many ways more serious than the actual therapeutic effect.

(*Dr Corbel*) That problem can now be overcome by the use of humanised monoclonal antibodies.

Lord Jenkin of Roding

737. The main thrust of your very interesting paper is that, in marked contrast to bacterial infections, on the whole vaccines are much less prone to provoking resistance. That is an encouraging message. But you suggest that there is the possibility of vaccine resistance due to antigenic variation. I am not sure whether that is the same as antigenic drift to which Dr Corbel referred some minutes ago. If this is happening as has been suggested in pneumococci and pertussis, is there other evidence of it? Is greater surveillance required? Is it an area where there needs to be more research?

(*Dr Schild*) It is a very important topic. I do not believe that there is any reason to be complacent and assume that problems of resistance to vaccination will never occur. It is rather early days. Widespread vaccination started only 40-50 years ago which can be seen as a rather short timespan. I believe that we should be sure that we have sufficiently intensive epidemiological surveillance to enable us to detect at a very early stage the emergence of antigenic mutants which may be selected by vaccination. Some observations give cause for thought. One of them is in Dr Corbel's field: the emergence of pertussis variants in Holland. These have led to suggestions that resistance to vaccination is occurring. Antigenic variants of hepatitis B virus have been observed in some countries. Whether these emerge as a result of vaccination is doubtful, but they merit considerable study. There are other examples.

(*Dr Minor*) There has been a great deal of interest in this on the part of those interested in vaccines. From time to time papers are published which suggest that something may be going on. For example, there is a discussion in America on measles isolates that potentially there is antigenic drift in measles following widespread vaccination in a way not observed before. There is an equally strong possible interpretation that that is completely wrong and that by vaccinating one

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DR GEOFFREY SCHILD and DR PHILIP MINOR

[Continued]

[Lord Jenkin of Roding *Contd*]

is eliminating certain genetic lineages of measles so it appears that there is a drift but that drift does not occur at all.

738. It may have been there all along. The organisms do not see the needle coming and say, "We must change"?

(*Dr Minor*) Exactly so. That probably applies across the board. The pertussis story is interesting but I do not believe that it is antigenic drift.

Lord Walton of Detchant

739. Effectively, do you mean that in the case of measles there are certain strains for which the original vaccine was not effective and that they have re-emerged?

(*Dr Minor*) No. The measles vaccine is effective for all measles strains that have ever been looked at. When one looks at the detailed responses to measles vaccine and the detailed immune responses to the different measles strains they can be told apart, if one looks hard enough. The implication was that by the use of measles vaccines one was seeing more and more of the strains which could be told a little bit apart from other strains.

(*Dr Corbel*) In relation to pertussis, there is no hard evidence that there has been vaccine failure as a result of micro-variation in the antigenic structure of the organism. There is much more concern in relation to the group B meningococci. For example, if vaccines based on class 1 outer membrane proteins were to be introduced they would probably drive antigenic variation perhaps even faster than occurs naturally. Vaccine resistance might then be a problem for those types of vaccines and one would need to change the formulation of the vaccine regularly to update them and incorporate new variants. But there are no confirmed examples of vaccine resistance so far.

Lord Rea

740. There was a minor leader in the BMJ recently about the rise in pertussis in Holland. Has Holland always had a higher rate of pertussis breaking through vaccine, or is it a new development? If so, what might it be?

(*Dr Corbel*) They have not always had a high rate. This appears to be a fairly new development. There are other problems associated with the vaccine and that may be to do with quality. That may have had an impact. The evidence that the vaccine variants are responsible for the breakdown is very much undecided.

741. Are you saying that there is a manufacturing problem in Holland as compared with other countries?

(*Dr Corbel*) I do not think that that would be publicly admitted but it is generally accepted.

(*Dr Schild*) The quality of vaccines is relevant to this issue. If vaccines are of limited potency they induce an immune response but not a fully protective immune response. This may foster exactly those conditions in which antigenic variants can arise and be selected for. The organism can replicate in the host but is selected in doing so. Ensuring that the vaccines used

are of high potency is a very important aspect of quality. We need increasing surveillance for the possibility of the emergence of variants that may grow through vaccine induced immunity because of the long lead time in vaccine development. If it emerges that variants are breaking through one may need to modify the composition of the vaccine to prevent it happening. That may involve re-establishing the safety and efficacy of the vaccine by clinical studies. We must know about the problem early if we are to combat it in time.

742. I presume that that is one of the reasons for your Institute's existence?

(*Dr Schild*) In part, but the Public Health Laboratory Service takes a lead on epidemiological surveillance. We work very closely with them.

Baroness Masham of Ilton

743. Is there going to be an H5N1 influenza pandemic?

(*Dr Schild*) It is a very interesting and difficult question. Up to now there have been 18 laboratory confirmed H5N1 infections in Hong Kong and none anywhere else. Six deaths have occurred. All of these infections could potentially have been acquired as a result of contact with infected chickens. There is no clear evidence of man-to-man transmission at the moment.

744. Were all of the people who died in contact with chickens?

(*Dr Schild*) Either directly or indirectly.

Lord Rea

745. Most Chinese people are in contact with chickens at some stage!

(*Dr Schild*) We do not know what is happening in South China at the moment, but a WHO delegation is there at the present. We have a situation in which a virus called H5N1 is capable of infecting man. It is a virulent virus and causes severe illness. There is no immunity to that virus in the population. It is a potential pandemic virus. What it does not seem to be able to do is transmit efficiently from man to man, which is good news. What happens in influenza is that if two influenza A viruses infect the same host they share their genes and there is genetic reassortment. If the H5N1 virus happened to infect the same individual as was infected with the current human epidemic virus called H3N2 or H1N1 it is possible that there would be genetic reassortment of viruses that would have the capacity to transmit effectively in man. Based on quite good circumstantial evidence, we believe that that was what happened in 1957 when the Asian influenza virus, H2N2, emerged. It caused global pandemics with much mortality. We believe that the ancestors of that virus were an animal or an avian influenza virus which recombined with the current human virus. We believe that a similar genetic interaction occurred in 1968 with the emergence of the Hong Kong virus, H3N2. There is also quite convincing genetic evidence that that virus was a reassortment between an avian

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DR GEOFFREY SCHILD and DR PHILIP MINOR

[Continued]

[Lord Rea Contd]

virus and a human virus. Because of the sophistication of genetic analysis now it is possible to predict which genes came precisely from the avian or animal progenitor and which came from the human virus. We shall be looking very hard to see what happens in Hong Kong. As we are approaching the influenza season there—the H3N2 virus is in circulation—there is a potential for this event to occur. It may not occur this year but in the next few years, but the potential is there.

Baroness Masham of Ilton

746. Has that virus passed from chicken to duck, turkey or other bird?

(Dr Schild) That is a possibility. The circumstantial evidence is that the cases in humans have coincided with an outbreak of the lethal H5N1 infection in chickens in Hong Kong.

747. Might the virus change?

(Dr Schild) Once the virus is established in man it will undergo progressive antigenic drift. Such drift will be monitored by the WHO influenza surveillance network which has 90 laboratories in many countries of the world and isolates influenza viruses and submitting them to international laboratories for detailed antigenic and genetic analysis.

748. It is a good example of how this present subject is a global problem?

(Dr Schild) The WHO influenza network is an example of international collaboration which time and time again has shown its value. It is because of this network that we can predict the antigenic composition of the epidemic strains from year to year and design vaccines in keeping.

Lord Walton of Detchant

749. Approximately how many influenza virus strains have been identified?

(Dr Schild) We classify influenza A viruses according to antigenic sub-types of haemagglutinin and neuraminidase. "H5" means "haemagglutinin antigenic sub-type 5" and "N1" means "neuraminidase sub-type 1". Among all the influenza A viruses that exist in birds, humans, horses and pigs there are 15 haemagglutinin sub-types and nine neuraminidase sub-types. So far few of the sub-types have been introduced into man. There are three human haemagglutinin sub-types (H₁, H₂ and H₃) and two neuraminidase sub-types (N₁ and N₂) so far.

Lord Rea

750. Over the years we have seen how comparatively rapidly new vaccines can be developed to counteract the new antigenic composition of viruses. How transferable are such techniques to other

micro-organisms that cause trouble which also have a shifting antigenic life history?

(Dr Schild) With reference to influenza?

751. I was thinking of using influenza as a model and applying the technique to other organisms to keep abreast of the ability of those organisms to adapt?

(Dr Schild) There are two types of antigenic diversity. One is a dynamic system as in influenza virus where one sub-type is rapidly replaced by another. In that case, using the same basic design of vaccine, one replaces the old antigen with a new one representative of current epidemic strains. The other type of diversity is when there are many antigenic sub-types of the organism which co-exist in pneumococcus, which Dr Corbel mentioned, or the hundred or so different varieties of common cold virus which co-exist with each other. It is very difficult to address the problem of such diversity in relation to vaccine design. You would need a hundred individual virus components in the vaccine for it to be effective. One is a diversity where the virus is selected by the immune system and the other is a constant diversity. Multi-valent vaccines are difficult and expensive to produce.

Lord Phillips of Ellesmere

752. We have heard a lot this morning about the importance of acquiring knowledge about various genomes in combating these infections. In the influenza virus not only do we know the genome structures but we know the detailed three-dimensional structures of both the neurominidase and the haemagglutinins. Does it mean that these problems are more easily addressed with influenza virus than some other agents where this information is so far lacking?

(Dr Schild) The enormous amount of detailed scientific information that we now have about influenza is beginning to contribute to vaccine design. For example, the influenza virus haemagglutinin can be expressed in insect cell systems in large amounts. People have successfully done this for the H5N1 virus haemagglutinin and prepared a biotechnologically-developed vaccine for evaluation. If it was successful it could be used to protect, say, people involved in manufacturing vaccine. The new knowledge is beginning to have practical applications. At the moment there are no radically new ways of designing influenza vaccine which enable us to overcome the problem of variation. Despite the sophistication of the knowledge—we know through crystallographic studies where the antigenic sites of the virus are, which aminoacids reside in those sites, which are the most and least variable and which are the receptor sites involved in the initial infection of the cell—we cannot predict what the next pandemic or even the antigenic drifted strain will be. We depend entirely on surveillance. I do not mean to be negative about this. We are getting better all the time but we are not there yet. More research is needed.

WEDNESDAY 4 FEBRUARY 1998

Present:

Dixon-Smith, L.	Soulsby of Swaffham Prior, L.
Jenkin of Roding, L	(Chairman)
Masham of Ilton, B	Walton of Detchant, L.
McFarlane of Llandaff, B.	Winston, L.
Platt of Writtle, B.	
Porter of Luddenham, L.	Phillips of Ellesmere, L.
Rea, L.	

Memorandum by the Department of Health

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Appendices (Not printed)

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Appendix B Hospitals referring VRE to the PHLS AR Laboratory.

Appendix C Number of Prescriptions.

Appendix D Net Ingredient Costs.

Appendix E Antibiotic Prescribing Items per Patients 1995-96 and 1996-97.

Appendix F Antibiotic Prescribing Guidelines for Common infections in General Practice.

Appendix G Drugs Used in the Treatment of Infections.

Appendix H National Prescribing Centre Combined Table of Contents 1994-96.

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INTRODUCTION

1. Resistance of micro-organisms to antimicrobial drugs has long been recognised. Some micro-organisms are inherently resistant to particular drugs. For instance, the resistance of *Mycobacterium bovis* to pyrazinamide is well recognised.

2. Of greater concern, however, is the ability of micro-organisms to develop resistance either through exposure to sub-lethal levels of antimicrobial drugs, or through the transfer of genetic material from already resistant organisms of the same or other species (the original organisms carrying the resistance not necessarily being pathogenic).

3. Although evidence of resistance began to emerge soon after the first antibiotics were introduced, a ready supply of new antibiotics kept pace with this tendency (between 1939 and 1972, over 30 new antibiotics were discovered). Since the early 1980s, far fewer new drugs have been available, and antimicrobial resistance has increased.

4. Serious drug resistant infections are commonest in hospitals, where high levels of antibiotic use allow the organisms to emerge and the close concentration of people with increased susceptibility to infection allows spread. Strains of some types of bacteria which are resistant to most or all of the drugs commonly used to treat them have become increasingly prevalent.

5. The importance of this issue both to individual and to the public health has increasingly been recognised in recent years, at national and international level, by scientists, Government and the public.

- In 1988, the World Health Organisation's European Office held a symposium on the Use and Abuse of Antibiotics Worldwide, which reviewed the relationship of antimicrobial resistance and the use of antimicrobials in a variety of types of infections. In particular it monitored the relation of aminoglycoside resistance to consumption patterns.
- A 1992 US report, *Emerging Infections: Microbial threats to health in the United States*,¹ included the development of resistance by microorganisms, as well as the emergence of new organisms, as areas for action.
- In his annual report for 1995 *On the State of the Public Health*,² the Chief Medical Office drew attention to the problem as a major issue of increasing importance requiring further work, and promised to report progress on the subject in future reports. He did so in his Annual Report for 1996 *On the State of the Public Health*,³ drawing attention to international concern on the subject; the free availability of antibiotics over the counter in many overseas countries; and the extension of their usage far beyond medical, dental and therapeutic veterinary practice because of their effect as growth promoters in agriculture.
- The World Health Organisation held a Scientific Working Group in November/December 1994 on monitoring and management of bacterial resistance to microbial agents which reported in 1995.⁴ The Group called for action on several fronts.

6. The World Health Assembly subsequently discussed the issue in 1995, and antimicrobial resistance was included among the problems to be addressed by the newly established WHO Division of Emerging, Viral and Bacterial Diseases Surveillance and Control (EMC). The threat of the growing resistance of common infectious diseases to antibiotics was the key subject of discussion at a meeting jointly organised by the World Health Organisation and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) in 1996, when agreement was reached on a framework for future collaborative efforts. Antibiotic resistant bacteria was also a major subject of discussion at the 1997 Congress of the European Society of Clinical Microbiology and Infectious diseases, where numerous delegates reported that the efficacy of most antibiotics was being threatened.

7. The problem is not so widespread in the UK as in many other countries, where antibiotics are more freely available and infection control procedures may be less effective. However, although the problem is one of international dimension requiring collaborative action, the UK cannot afford to be complacent.

EXTENT AND TRENDS

General Position

8. Most species of bacteria have the ability to develop resistance to antibiotics if they are exposed to these drugs for periods of time or at dosages which are insufficient to kill them. This resistance may then, in some cases, be transferred to other species of bacteria, usually via genetic material in plasmids, which are loops of DNA separate from the bacterial chromosome. Plasmids commonly encode resistances to multiple different antibiotics, together with genes that facilitate their own transmission. The original emergence of plasmid mediated resistance is rare. It is impossible to give a simple numeric frequency because the frequency of transfer varies with the particular plasmid, host species and the conditions. But what is clear is that plasmids can allow

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very efficient spread. To give one example: ampicillin was introduced in 1963 as the first broad-spectrum penicillin. Virtually all *Escherichia coli*, *Haemophilus influenzae* and *Neisseria gonorrhoeae* were susceptible.

E. coli strains with a plasmid-coded ampicillin-destroying enzyme "TEM-1 β -lactamase" were recognised in 1965. During the late 1960s and early 1970s plasmids coding this enzyme spread widely among *E. coli* and related species; by the mid-1970s they had reached *H. influenzae* and *N. gonorrhoeae*. Now, about 40-60 per cent of *E. coli* isolates in the UK have TEM-1 β -lactamase, and its contingent resistance, as do 10-15 per cent of *H. influenzae* and 5-10 per cent of *N. gonorrhoea* (rates in the latter species are higher (up to 30-50 per cent) in Southern Europe and South East Asian countries). The result is that ampicillin has been "lost" or impaired as a cheap reliable treatment for urinary tract infection (where *E. coli* is the commonest pathogen); in acute exacerbations of bronchitis (where *H. influenzae* is common) and in gonorrhoea. New variants of TEM-1, now spreading, give resistance to cephalosporin antibiotics that were designed to escape destruction by the parent form of this enzyme.¹

Data Collection

9. Information on the extent and trends of resistance to antimicrobial agents comes from national and international surveillance systems, from individual studies and from spontaneous case or laboratory reports. The collection of accurate and comparable data for surveillance purposes on the extent of the problem and recent trends, is hampered by several constraints. Nonetheless, a considerable bank of national and international information has been collected and published. The factors that need to be borne in mind when developing surveillance systems, include:

- results reported from different laboratories may not be comparable: they may have used different methods of testing, or different cut-off points in the same text for defining resistance;
- different laboratories may test against different antimicrobial agents;
- lack of accurate data on denominator populations;
- studies may be restricted to special population groups, e.g., in hospital, where more antibiotics are used and rates tend to be higher, rather than in the community;
- lack of comparability between study populations in geography or time.

10. The following paragraphs summarise information concerning some individual organisms or infections and some more general situations. The Public Health Laboratory Service (PHLS), in its written evidence to the Sub Committee, provides detailed data on the current extent and trends in antimicrobial resistance in the UK.

STAPHYLOCOCCAL INFECTIONS (INCLUDING METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) AND MULTIDRUG RESISTANT MRSA)

11. *Staphylococcus aureus* is a common organism. About one-third of the population carry it on the skin or in the nose and throat. However, if there is reduced resistance to infection and the bacteria enter the body, for instance through a surgical wound, it can cause more serious infections such as septicaemia or pneumonia.

12. Methicillin resistant *Staphylococcus aureus* is an antibiotic resistant variety of the bacterium and behaves in exactly the same way. Methicillin resistant strains first emerged in 1961 (in the UK) following the introduction of methicillin into clinical use. Reports from other European countries, Asia, Australia and South Africa soon followed. Many strains are now resistant not just to methicillin but to most other antibiotics, and MRSA are currently the most widespread multiply drug resistant organisms in the UK. They are not a significant risk to healthy people, hence they are not a hazard in the community, but in hospital patients they can cause a range of problems from trivial skin infections to septicaemia.

13. There is no evidence that MRSA have a greater capability to cause more infection than strains of the same bacterium which are not resistant to antibiotics, but treatment of these infections is much more difficult. There are also epidemic strains of MRSA which spread very readily from person to person. Eight per cent of people carrying such strains are only "colonised", that is they have no evidence of infection and are therefore not easily identifiable before spread to patients has occurred.

14. The extent to which MRSA cause invasive infection can be gauged from their presence in isolates from blood or cerebrospinal fluid. Between 1989 and 1995 about 200 clinical laboratories in England and Wales reported their results of susceptibility testing of between 4,501 and 6,370 such isolates a year. Resistance to methicillin remained at about 1.5 per cent until 1991, but then increased to 13.2 per cent in 1995. At the same time there was a significant increase in the percentage of isolates resistant to erythromycin, clindamycin, ciprofloxacin, gentamicin, trimethoprim and rifampicin.⁵

¹ Data supplied by Public Health Laboratory Service Antibiotic Reference Unit.

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15. A total of 189 hospitals in England and Wales are known to have had "incidents" of MRSA in 1995 (an incident is three or more patients colonised or infected with the same strain of MRSA within a month), compared with 125 hospitals in 1992. It is by far the commonest cause of outbreaks which necessitate the temporary closure of wards and other disruption to a hospital's routine services. Recent PHLS surveillance data on MRSA is shown in Appendix A.

16. MRSA has, up to now, remained sensitive to vancomycin. Since recognition of vancomycin-resistant enterococci (see paragraphs 18 and 19), the possible transfer of vancomycin resistance to *S aureus* has been anticipated, with serious consequences for treatment. The first documented cases of infection cause by *S aureus* with reduced susceptibility to vancomycin have now been reported from Japan⁶ and the United States.⁷

OTHER MULTIPLY ANTIBIOTIC RESISTANT HOSPITAL ACQUIRED ORGANISMS

17. A number of other multiply resistant bacteria are increasingly seen in specialist hospital units. Most of these organisms are not sufficiently virulent to cause illness except in patients with grossly depressed immune systems, such as those on transplant or in intensive care units. Outbreaks have less potential to disrupt the whole hospital, but are still serious, both in terms of avoidable morbidity and mortality and because of the effects on other patients if the unit has to be closed. There may be a lack of alternative specialist facilities for other patients of these units.

STREPTOCOCCAL INFECTIONS

Vancomycin Resistant Enterococci

18. Enterococci are bacteria which are part of the normal flora of the human gut. Ninety per cent of laboratory isolates of these organisms are from patients who are simply carrying the organisms, and have no evidence of active infection due to them. They are a risk mainly to patients in specialist hospital units such as kidney dialysis and bone-marrow transplant units. If the organisms gain access to normally sterile parts of the body in these vulnerable patients they can cause a range of different types of infection, from superficial infection of skin wounds to urinary infections and septicaemia. Serious infections (e.g. septicaemia) can be extremely difficult to treat because the bacteria are often resistant to all "standard" antibiotics.

19. The emergence of vancomycin resistant enterococci (VRE) is of particular concern, firstly because of the fear that the genetic material which carries the vancomycin resistance may transfer from them into MRSA (making MRSA virtually untreatable) (see above) and secondly because of speculation that humans may acquire them by eating food derived from animals which have been given similar antibiotics as growth promoters. VRE have been isolated from meat in the UK and other countries and it has been postulated that farm animals receiving the growth promoter avoparcin could be a source of VRE in man. Because of these concerns, the European Commission banned the use of avoparcin as a growth promoter in Member States from 1 April 1997. VRE infections are as yet relatively uncommon. Risk factors include critical illness and prolonged hospital stay, as well as the use of vancomycin. In at least half of bloodstream infections associated with VRE, and probably in a similar proportion of other types of infection, other bacteria, often of a greater virulence, are also present and are probably the primary cause of infection. PHLS surveillance data on the number of hospital reporting VRE is shown in Appendix B.

Streptococcus pneumoniae (pneumococcus)

20. Pneumococci are common commensal organisms in the upper respiratory tract—that is they are commonly carried without causing disease. They are also among the commonest causes of community acquired bacterial infection (pneumonia, middle ear infections and meningitis) and of respiratory infections acquired in hospital.

21. Initially all pneumococcal isolates were susceptible to penicillin, which was the treatment of choice. The first strains of pneumococci resistant to penicillin were isolated in the mid 1960s. Subsequently, resistant isolates have been reported with increasing frequency from all parts of the world, so that susceptibility to penicillin, cephalosporin and macrolide antimicrobials can no longer be assumed, although the prevalence has remained low in northern Europe. In 1977, outbreaks of multi-drug resistant pneumococci occurred in South African hospitals some of which have since been reported from other countries.

22. In 1994, 2.5 per cent of bacteraemia and meningitis isolates (i.e., isolates from the most severe pneumococcal infections) reported to the PHLS in England and Wales showed full of intermediate resistance to penicillin and 11.2 per cent were resistant to erythromycin.⁸ This compares with rates of up to 50 per cent in some other parts of Europe and the USA.

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23. Resistance to penicillin among pneumococci is due to an alteration of up to six penicillin-binding proteins, acquired by transformation or mutation. Resistance is, however, not necessarily total and may be overcome by larger doses of antibiotic. There is some evidence of geographic variation in prevalence, with higher levels being reported from east London and Merseyside.⁹ The reports emphasise the importance of continued local as well as national surveillance of resistance among pneumococci, and the need for further work into trends and risk factors. The influences of different serotypes, travel and patterns of antimicrobial prescribing are some of the areas requiring further investigation.

24. A study from Iceland and Finland published in 1996¹⁰ showed a strong association between antimicrobial use, both individual and total antimicrobial consumption in the community, and nasopharyngeal carriage of penicillin resistant pneumococci in children. The authors recommended that control measures to reduce this prevalence should include restricting the use of antimicrobials in community health care.

TUBERCULOSIS

25. The ability of *M. tuberculosis* to develop resistance to treatment was recognised shortly after the introduction of the first antituberculosis drugs in the 1950s. It rapidly became apparent that the treatment of tuberculosis required a combination of drugs over a prolonged period of time in order to achieve cure and prevent the emergence of drug resistance. Following large scale trials, standard treatment protocols are now well established, but prevention of the emergence of resistance still requires that:

- the correct drugs are prescribed for the correct duration of time (normally at least six months);
- supply of these drugs is maintained throughout the treatment period;
- the drugs are of approved quality, containing the correct amount of active ingredient;
- the patient takes the treatment compliantly;

and also that antituberculosis drugs are not freely available for self medication (for example, some over-the-counter cough linctuses in India are known to contain small amounts of antituberculosis drugs, of no therapeutic value but ideal for promoting drug resistance).

26. The introduction of rifampicin into treatment protocols for tuberculosis enabled treatment courses to be reduced from 12–18 months to the current six months. However, since its introduction, multiple drug resistant strains of tuberculosis (by definition, resistance to rifampicin and isoniazid, the two most effective drugs against tuberculosis, with or without resistance to other drugs) have emerged world-wide. Drug resistant tuberculosis is difficult to treat, may be unsuspected, so that patients may initially receive inappropriate treatment. Longer treatment will then be required. For these reasons, patients are likely to remain infectious for longer, increasing the chance of drug-resistant infection being passed on to other people.

27. Most hospital laboratories in England and Wales submit isolates of *M. tuberculosis*, and other mycobacteria, to one of the PHLS Regional Centres for Mycobacteriology or the Mycobacterium Reference Unit, for speciation and drug sensitivity testing. In Scotland, isolates are sent to the Scottish Mycobacteria Reference Laboratory in Edinburgh. In Northern Ireland, speciation and antibiotic susceptibility patterns are determined by the Northern Ireland Mycobacterial Reference Library. Collation of the information on drug sensitivity was not routinely carried out during the 1980s but was reviewed in a study published in 1993.¹¹ Out of approximately 2,000 initial isolates of *M. tuberculosis* submitted each year to the PHLS laboratories between 1982 and 1991, approximately 10 per cent were found to be resistant to one or more first line anti-tuberculosis drugs, including 6 per cent resistant to isoniazid (with or without resistance to other drugs) and 0.6 per cent resistant to isoniazid and rifampicin (with or without resistance to other drugs). No increasing trend was apparent in these data. The National Surveys of Tuberculosis Notifications in 1978–79, 1983, 1988 and 1993 also examined the occurrence of drug resistance but in previously untreated patients with pulmonary disease only. Rates of drug resistance were found to be very low with no increasing trend. Drug resistance rates were found to be higher in immigrant groups than in the indigenous white population.

28. With the emergence of drug resistance in tuberculosis as a problem world-wide, the PHLS, in co-operation with the Scottish Centre for Infection and Environmental Health, has instituted an active surveillance scheme for drug resistance in isolates submitted from patients in England, Wales, Scotland and Northern Ireland—the UK Mycobacterial Resistance Network (MYCOBNET). Data from this scheme for 1994 have been compared with data from the National Tuberculosis Notification Surveys of 1988 and 1993. Resistance to isoniazid (with or without resistance to other drugs) was reported in 5.8 per cent of initial isolates in 1994, compared with 4.7 per cent and 3.9 per cent in 1993 and 1988 respectively (PHLS unpublished data). Resistance to rifampicin was found in 1.9 per cent, 0.9 per cent and 0.7 per cent of initial isolates in 1994, 1993 and 1988 respectively. Multiple drug-resistance was found in 1.5 per cent, 0.8 per cent and 0.6 per cent of initial isolates in 1994, 1993 and 1988 respectively.

29. Resistance to isoniazid in 1994 was higher in England (5.9 per cent) than in Scotland (4.5 per cent) or Wales (2.8 per cent); in Northern Ireland it was 10.0 per cent, but this was based on only 51 isolates and with

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such small numbers there is marked variation in resistance levels. In the English regions, isoniazid resistance was highest in the two Thames regions (South Thames 7.6 per cent, North Thames 7.1 per cent) followed by Anglia and Oxford (6.0 per cent). Isoniazid resistance in the remaining regions was 5.1 per cent or below. Resistance to isoniazid in 1994 was higher in patients born abroad (9.5 per cent) than those born in the UK (4.5 per cent), but place of birth was not reported for 64 per cent of cases. Isoniazid resistance was highest in those of African ethnic origin (13.0 per cent), followed by Oriental ethnic origin (9.1 per cent), Indian subcontinent ethnic origin (7.5 per cent and white ethnic origin (4.4 per cent). Ethnic origin was not reported in 27 per cent of cases. Isoniazid resistance was higher in the 180 patients reported to be HIV seropositive (11.1 per cent) than in the 3,106 patients in whom HIV status was not reported (5.4 per cent).

30. These results suggest an increase in the number of drug-resistant cases in the UK in recent years but will need to be confirmed by further monitoring over the next few years by the MYCOBNET system. The results are consistent with the increase in the proportion of tuberculosis cases generally in England and Wales arising in individuals from ethnic minority populations among whom drug resistance is recognised to be more common. The suggestion of higher rates of drug resistance in the HIV positive group, which echoes results from several other European countries (unpublished data), is particularly concerning and requires careful monitoring.

Outbreaks of drug resistant tuberculosis

31. Outbreaks are a well recognised feature of the transmission of tuberculosis in the community, usually arising as a result of infection from a patient with sputum smear positive pulmonary disease and a cough. Outbreaks of drug resistant tuberculosis have occurred from time to time since the introduction of anti-tuberculosis drug therapy. The advent of the HIV epidemic has led to the assembling of immunocompromised HIV infected patients, who are at increased risk of developing tuberculosis following infection, in institutions such as hospitals (sometimes referred to as "immunocompromised convergence"). Internationally, this resulted in a large increase in the number of outbreaks reported in the late 1980s and early 1990s, particularly from the United States but also from Europe, mainly involving HIV infected patients, and of both drug sensitive and drug resistant disease. Two outbreaks of multidrug resistant tuberculosis have recently occurred in London hospitals, largely affecting HIV infected individuals. The index case in one had acquired MDR-TB abroad; the other had developed drug resistance through poor compliance with treatment for initially drug sensitive disease. An aggravating feature of most nosocomial (hospital acquired) outbreaks of tuberculosis has been a breakdown in hospital infection control measures.

SALMONELLA AND OTHER GASTROINTESTINAL PATHOGENS

32. Salmonella and Campylobacter are the most frequently isolated bacterial pathogens associated with acute gastroenteritis in humans in UK. *Escherichia coli* O157, although not as frequent as Salmonella and Campylobacter in terms of laboratory reports, is also important because of its potential to cause severe disease in humans. Salmonella infections have increased dramatically in the last 10-15 years.

33. Most Salmonella, Campylobacter and *E. coli* occur in animals where they are usually carried asymptomatically in the gastrointestinal tract and may enter the food chain through animal products. Human infection is usually foodborne, but may follow contact with animals or person to person spread. By contrast, *Salmonella typhi* and *Salmonella paratyphi* A and B, the cause of typhoid and paratyphoid fevers, are usually found only in humans and higher primates, and most human infections are acquired outside the UK, directly or indirectly from infected people or carriers.

34. Antibiotic resistance in bacterial enteric pathogens may be constitutive, or induced following exposure to antimicrobials used in veterinary medicine, agriculture or human medicine. In salmonellas, multiple drug resistance is prevalent in human isolates of *S. typhi* as well as in *S. typhimurium*, *S. hadar* and *S. virchow*. Multiple antibiotic resistant *S. typhimurium* DT104 was initially identified in cattle in England and Wales in 1988. Subsequently it was isolated from poultry, sheep, pigs and horses. It is now the second most prevalent Salmonella reported from humans in the UK after *S. enteritidis* PT4., with a 10-fold increase in the number of human cases reported between 1990-96 (from 300 to 3,500 cases per year). An increase in multi-drug resistant *S. typhimurium* DT104 is also reported from other European countries.

35 The majority of human isolates of Campylobacter are resistant to one or more antibiotics with a significant proportion resistant to ciprofloxacin. In human isolates of *E. coli* O157, resistance to at least one antibacterial has increased since 1992 but multiple drug resistance remains rare.

SEXUALLY TRANSMITTED INFECTIONS-GONORRHOEA

36. Gonorrhoea is caused by *Neisseria gonorrhoeae*. Due to the spread of resistant strains worldwide, WHO no longer recommends penicillin as the first line drug for gonorrhoea. Resistance to penicillin can also be accompanied by reduced sensitivity of organisms to other antibiotics, for example ciprofloxacin has good activity against gonococci but more than 10 per cent of penicillinase producing *N. gonorrhoeae* (PPNG) strains isolated in 1996 were also resistant to ciprofloxacin. Resistance to penicillin in PPNG strains and also high levels of tetracycline resistance are due to plasmid acquisition. Resistances to other antibiotics are caused by chromosomal

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mutations. Resistance to penicillin may also be chromosomally mediated and there is some evidence that such strains (CMRNG) may be slightly less susceptible to ceftriaxone and are considerably less susceptible to cefuroxime.

Incidence of gonorrhoea in England and Wales

37. Most diagnosed cases of gonorrhoea are treated in genitourinary medicine (GUM) clinics but infections, especially in women, can be asymptomatic and may not be diagnosed. Data based on GUM clinic returns provided to the Department on form KC60 shows that following a decline in new cases of uncomplicated gonorrhoea in the early 1990s, cases increased in 1996 for the second consecutive year. In men, 7,754 cases were reported in 1996 compared with 6,634 in 1995, a 17 per cent increase; new cases in females rose by 13 per cent (from 3,340 cases to 3,786 cases).

Resistance and clinical practice

38. Clinical practice in the UK has to respond to changes in the antibiotic resistance of *N. gonorrhoeae* in the UK population. Antibiotic resistant strains are not a significant problem in the UK and are usually encountered in patients infected abroad. Therefore, unless the case history indicates that infection may have been acquired abroad in areas where there is a greater prevalence of antibiotic resistant strains, standard clinical practice in the UK is to treat gonorrhoea with amoxycillin with probenecid.¹ If the patient does not immediately respond to treatment, the possibility of infection with penicillin resistant strains is considered. Penicillin is not usually employed in the UK for returning travellers. Although antibiotic resistant strains of this organism exist they are not yet a significant clinical problem in the UK but continued surveillance is required.

Laboratory reports of antibiotic resistant isolates of Neisseria gonorrhoeae

39. Data on antibiotic resistant isolates of *N. gonorrhoeae* are provided by the PHLS Gonococcus Reference Unit (GRU) at Bristol PHL. The GRU received 490 antibiotic resistant isolates in 1996, the largest number since 1988. All reports were followed up by a questionnaire to determine where the infection was acquired, sexual orientation, site of infection, and demographic characteristics. There were 333 isolates from men, 110 from women, and for 47, the individual's sex was not stated. The modal age group for female cases was 20 to 24 years and for male cases was 25 to 34 years (see table 1 below).

TABLE 1

Number of antibiotic resistant strains of Neisseria gonorrhoeae received by the GRU by age group (years) and sex in 1996

Sex	< = 15	16-19	20-24	25-34	> 35-44	> = 45	not reported
Males	2	18	64	141	65	33	10
Females	5	17	35	33	8	7	5

40. The ethnic origin and the region where infection was acquired were recorded for 331 cases (68 per cent) (see table 2 below). Of these 331 cases, 242 (73 per cent) probably acquired their infection in the United Kingdom (UK) which indicates that spread of resistant strains in the UK is possible and surveillance is required to monitor the situation.

TABLE 2

Number of antibiotic resistant N. gonorrhoeae strains by geographic area where infection was acquired and ethnic origin of patients: 1996

Area infection acquired	White	Black Caribbean	Black African	Asian	Other	Total Per cent
Far East	31	—	—	5	1	37 (11)
Africa	9	—	12	—	—	21 (6)
Caribbean	4	6	—	—	—	10 (3)
Europe	11	—	—	—	—	11 (3)
UK	186	42	8	3	3	242 (73)
Other	6	1	—	2	1	10 (3)
Total (Per cent)	247 (75)	49 (15)	20 (6)	10 (3)	5 (2)	331 (100)

¹ Probenecid reduces antibiotic excretion and hence increases blood concentrations.

41. Since 1989, more multi-resistant strains have been reported and the number of penicillinase producing (PPNG) isolates without plasmid mediated resistance to other antibiotics has declined. In 1996 more PPNG isolates with plasmid associated high level tetracycline resistance (PPNG/TRNG) were reported than penicillin resistant strains alone. Tetracycline resistant (TRNG) isolates rose in 1996 and equalled the number of PPNG/TRNG isolates (see table 3 below). In 1996 five PPNG strains had high level resistance to tetracyclines and reduced susceptibility to ciprofloxacin, but no PPNG strains were detected that had high level resistance to both tetracyclines and ciprofloxacin. Twenty-five strains were resistant to ciprofloxacin, 17 of these has plasmid associated resistance and three chromosomally mediated resistance to penicillin.

TABLE 3
Plasmid mediated antibiotic resistance: isolates reported 1988 to 1996

Year	1988	1989	1990	1991	1992	1993	1994	1995	1996
PPNG	156	214	207	186	192	126	85	96	70
PPNG/TRNG	0	0	22	80	93	57	90	121	94
TRNG	4	1	11	15	47	35	46	57	94

PPNG penicillinase producing *N. gonorrhoeae*.
PPNG/TRNG penicillinase producing and high level tetracycline resistant *N. gonorrhoeae*.
TRNG high level tetracycline resistant *N. gonorrhoeae*.

42. In 1996, chromosomally mediated penicillin resistant *N. gonorrhoeae* (CMRNG) isolates rose to more than double the 1995 figure, and 148 (69 per cent) of the 213 isolates in 1996 were acquired in the UK (see table 4 below).

TABLE 4
Chromosomal mediated antibiotic resistance: isolates reported 1988 to 1996

Year	1988	1989	1990	1991	1992	1993	1994	1995	1996
CRNG	—	2	5	9	10	13	17	29	44
CRNG & PPNG	1	16	30	26	24	7	17	32	26
CMRNG	65	47	94	71	51	98	90	106	213

CRNG Chromosomally mediated ciprofloxacin resistant *N. gonorrhoeae*.
PPNG/CRNG Penicillinase producing *N. gonorrhoeae* (plasmid) with decreased susceptibility to ciprofloxacin (chromosomal).
CMRNG Chromosomally mediated penicillin resistant *N. gonorrhoeae*.

RESISTANCE TO ANTIVIRAL AGENTS

43. In the last few years, important advances have been made in the treatment of viral infections with the introduction of several antiviral drugs. Viral resistance may emerge against virtually all antiviral compounds, and both selection and transmission of resistant viruses can be anticipated.

Influenza

44. The antiviral agents amantadine and rimantadine are active against influenza A and may be used either prophylactically, to prevent infection in an outbreak, or for treatment, to shorten the length of illness. They are currently little used, but could take on increasing importance in the face of a widespread or severe epidemic or pandemic of influenza. Some limited data suggest that if used for prophylaxis and treatment in the same household, resistance to amantadine can emerge. This would require monitoring if widespread use of these agents were to be recommended. New antiviral agents against influenza are currently under development and resistance in them will also require monitoring, once they are introduced.

HIV/AIDS

45. Two groups of anti-retroviral drugs are used against HIV: reverse transcriptase inhibitors and protease inhibitors, each acting at different stages of the virus replication cycle. HIV is a virus with a high mutation rate, particularly in the genes that code for reverse transcriptase (RT). This means that variants that are resistant to RT inhibitor drugs arise spontaneously and even more frequently in the presence of the drug.

46. The current clinical consensus is that two or more drugs should be used simultaneously so as to inhibit the development of viral resistance,¹² moving away from monotherapy with zidovudine (AZT) to drug combinations such as zidovudine plus didanosine, or zidovudine plus didanosine plus indinavir.

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47. There are anecdotal reports from clinicians of diminishing anti-retroviral effect of AZT in individual patients and, in the US, on-going clinical trials suggest that AZT resistance is clinically significant and associated with an increased risk of disease progression. There are also reports of cross-resistance occurring between different protease inhibitor drugs.

48. In the UK there is at present no routine surveillance for HIV resistance to these antiviral agents, although the PHLS has set up an Antiviral Susceptibility Reference Unit in Birmingham and the Department of Health is discussing a project to study the geographical and temporal differences in HIV drug resistance and the implications for post exposure prophylaxis policy.

RESISTANCE IN FUNGAL AND PROTOZOAN INFECTIONS

Cryptosporidium

49. Cryptosporidiosis is a water-borne gastrointestinal infection, outbreaks of which have been associated with farm visits and with contaminated drinking water. An effective antimicrobial against cryptosporidium has yet to be found because of its inherent natural immunity.

Malaria

50. The increasing resistance of malaria, and particularly the more severe falciparum form, poses problems for control, for treatment and for the prevention of malaria in travellers. Resistance to chloroquine continues to spread and to become more complete in the areas where it occurs. Chloroquine resistant vivax malaria, previously very uncommon, is also now emerging in South-East Asia. The alternative antimalarials are few, and, while all antimalarials are associated with adverse reactions in a proportion of recipients, they may be associated with a different spectrum of reactions which may be less well tolerated by travellers. Mefloquine, for example, the most effective antimalarial for many travellers to chloroquine resistant areas, may be associated with neuropsychiatric reactions such as bad dreams, anxiety, depression and convulsions.

51. Resistance of falciparum malaria to drugs other than chloroquine is already a major problem in South East Asia and is becoming more common elsewhere. A careful assessment of the balance of risk of malaria against the risk of the adverse reactions to the available antimalarials is now necessary when advising travellers. The decisions are increasingly difficult to make and new drugs are urgently needed.

ANTIMICROBIAL SUSCEPTIBILITY IN PATHOGENIC BACTERIA FROM FARM ANIMALS

52. Pathogenic bacteria (e.g., Staphylococci, Streptococci, *E. coli*, Pasteurella) isolated from farm animals during the course of diagnostic work are tested for their susceptibility to a range of antimicrobials by the Veterinary Investigation Division of the Veterinary Laboratories Agency to assist the veterinary practitioner in his choice of therapy. The report is sent to the practitioner and the results filed at the Veterinary Investigation Centre.

Salmonellas

53. All *Salmonellas* received for serological identification at the Central Veterinary Laboratory are tested for their *in-vitro* sensitivity to 16 antimicrobials. All the isolates come from farm animals and their environment in England and Wales. The choice of antimicrobials, which is periodically reviewed, is designed to comprise a core set which has been used in veterinary practice for many years, some of the more recently licensed antimicrobials and some which are permitted in other European countries. Monitoring has been carried out since 1971 and the results published periodically in the scientific press. Annual reports are found in "Salmonella in Livestock Production" published by the Veterinary Laboratories Agency.

54. The results for 1996 show that 48 per cent of the 5,789 salmonellas tested are susceptible to all the antimicrobials used for testing. However, only 10.8 per cent of the 2,323 *S. typhimurium* tested are fully susceptible. Of the *S. typhimurium* cultures, 74 per cent were the multiple resistant phage type DT104.

Escherichia coli 0157

55. Multiple resistant isolates of *E. coli* 0157 have not been detected and all the cultures tested so far have been susceptible to most of the antimicrobials used for testing.

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PREVENTION AND CONTROL OF ANTIMICROBIAL RESISTANCE

Factors leading to the emergence and spread of antimicrobial resistant organisms

56. Some of the issues at the centre of discussion are:

- the extent of the use of antimicrobials in humans;
- uncontrolled over-the-counter sales of antibiotics in some countries;
- the role of international travel in the spread of resistant microorganisms;
- the difficulties in producing new antibiotics;
- their increasing use in animal husbandry, and their presence in foodstuffs.

Department of Health mapping exercise

57. Following CMO's identification in his 1995 Annual Report of antibiotic resistant bacteria as a key issue for further work, a small project team was set up in the Department to undertake an internal mapping study to provide an overview of the many interests of the antibiotic-resistant micro-organisms within the Department, and form a basis for internal discussion on how best to develop a strategic approach to antimicrobial resistance. That work is continuing. One outcome, following discussion by the Department's Standing Medical Advisory Committee (SMAC), was the setting up of a SMAC sub group to look at the clinical use of antimicrobial drugs in relation to antimicrobial resistance (see paragraphs 92-93).

Elements of a strategy

58. A comprehensive prevention strategy for antimicrobial resistance needs to include consideration of:

- infection control measures;
- surveillance;
- rational antibiotic use in clinical practice;
- the use of antimicrobials in veterinary practice and animal husbandry immunisation policy;
- the need for and use of rapid diagnostic tests;
- drug development;
- vaccine development;
- the need for other research;
- international collaboration.

Some of these are looked at in more detail below.

SURVEILLANCE

59. Surveillance provides the information on which to base control measures and includes the elements of data collation, analysis and interpretation as well as dissemination of the results to those who need them. The integration of epidemiological and laboratory sciences are critical in the prevention and control of antimicrobial resistance, surveillance needing to cover the incidence of infections, as well as the prevalence of resistant organisms and their antimicrobial resistant patterns in different subsets of the population. Local needs may be different from national ones.

60. The Public Health Laboratory Service (PHLS) has increased its surveillance and monitoring of drug resistance in several areas in recent years. An example is the surveillance of drug resistance in isolates of *M. tuberculosis* in the UK using the MYCOBNET system described in paragraph 28.

PRESCRIPTION AND USE OF ANTIBIOTICS

Introduction

61. The role of the use of antimicrobials in the development of antimicrobial resistance is undoubted. Those countries with high usage and uncontrolled availability of "over the counter" antibiotics tend to have higher levels of antimicrobial resistance, whereas Denmark, for instance, has seen a dramatic reduction in the prevalence of antibiotic resistant micro-organisms since tight controls on antimicrobial usage, together with strict infection control procedures, were introduced. Similarly, in Finland, greatly reduced levels of erythromycin resistant

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Group A streptococci from throat and pus cultures (from 19 per cent in 1993 to 8.6 per cent in 1996) coincided with reduced use of macrolide antibiotics following the introduction of guidelines recommending curtailing the use of erythromycin and other macrolides for outpatient respiratory and skin infections.

ANTIBIOTIC PRESCRIBING BY GPs IN THE UK

Overview

62. The Government's policy on prescribing is based on the principles that patients should have access, through the NHS, to effective drugs to meet real clinical need, and that the provision of those drugs should be safe, appropriate and cost-effective. The aim of this policy is to encourage rational and cost-effective prescribing to fulfil these principles. The focus on promoting rational and effective prescribing is at the level of clinical practice, both in General Practice and in hospital. It is here that the clinical needs of patients can best be identified and decisions on appropriate drug therapy made. The policies in place are designed to support and reinforce this approach. Antibiotic prescribing policies have been developed within this framework, particularly concentrating on measures to discourage unnecessary or inappropriate prescribing. Antibiotics (other than some topical, ENT and vaginal preparations) are Prescription-only Medicines and may be prescribed by GPs. Antibiotics are not included in the Nurse Prescribers' Formulary.

Statistics

63. The two tables attached as Appendices C and D give information respectively on the number of prescriptions and net ingredient cost of antibacterial (BNF 5.1), antiviral (BNF 5.3) and antiprotozoal (BNF 5.4) drugs dispensed in England between 1980 and 1996. For comparison, similar information on the total of all drugs (excluding dressings and appliances) is included. Unfortunately, data up to 1990 are not consistent with those for 1991 onwards.

64. Between 1991–1996, the number of prescription items for antibacterial drugs (BNF 5.1) increased by just under 7 per cent compared to 19 per cent for all drugs. However, the increase over the period varied considerably within this therapeutic group. Over the same period, the net ingredient cost rose by 4 per cent compared to 59 per cent for all drugs.

Again, the increase varied by therapeutic group. There were reductions in both volume and cost (6 per cent and 9 per cent respectively) between 1995 and 1996.

65. The area of growth that gives most cause for concern is that of 4-quinolones (BNF 5.1.12). Over the last five years there has been a substantial increase in use and cost (up 48 per cent and 81 per cent respectively). Overuse in the community for non-specific infections could lead to resistance and reduce the effectiveness in the treatment of life-threatening infections in seriously ill hospitalised patients. Ciprofloxacin is the market leader in a group of drugs which is heavily promoted.

66. The increasing use of penicillins (BNF 5.1.1)—up by 3 million items (13 per cent) over the five-year period—is disappointing. Potentially, this may result from demographic factors (more young and elderly) or it may represent some evidence of increasing resistance (patients needing a second course of treatment).

67. The decrease in the use of Sulphonamides and Trimethoprim (BNF 5.1.8)—down 33 per cent—is probably related to the Committee on Safety of Medicine's advice that the risk benefit ratio of sulphonamides is such that their use should be restricted to a very limited number of indications only.

68. Whilst the use of Clindamycin and Lincomycin (BNF 5.1.6) is low, it did increase by 112 per cent over the five-year period. Concerns about toxicity led to reduced use during the 1980s. The recent increase is probably due to specialist-initiated prescribing continued by the GP.

69. Macrolides (BNF 5.1.5) show a substantial increase in cost (58 per cent or £11 million), but marginal increase in use. The newer (and more expensive) macrolides are licensed for use in *H. pylori* eradication and it seems likely that declining use of the originator product (erythromycin) is being balanced by use for the new indication. The newer macrolides are heavily promoted.

70. Other antibiotics (BNF 5.1.7) have increased in cost terms by 114 per cent (increased use 56 per cent)—hospital-initiated prescribing, continued by GPs, is a potential explanation, e.g., colomycin for cystic fibrosis patients.

Health authority variations in antibiotic use

71. The graphs attached as Appendix E provide a comparison of antibiotic prescribing between health authorities for the two years 1995–96 and 1996–97. The information is shown on an "items per patient" basis. The analysis reveals marked variations between authorities, with prescribing at the upper end of the scale double that at the lower end.

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72. The Department is hoping to co-operate with the Unit of Health-Care Epidemiology (Institute of Health Sciences, Oxford University) in a study relating the variations in antibiotic use to variations in antibiotic resistance around the country. The proposed analysis would determine to what extent districts with higher antibiotic utilisation have higher levels of resistance. It will provide a useful first step in determining whether the level of community antibiotic utilisation affects the level of antibiotic resistance.

Local policies on antibiotic prescribing

73. The Government considers that detailed national guidance on the prescribing of antibiotics to individual patients would not be appropriate because of local variations in resistance patterns. The doctor with clinical responsibility for the patient is best placed to decide the most appropriate treatment. Local microbiologists and physicians responsible for the control of infectious diseases should provide information to doctors on local bacterial resistance with advice on antibiotic use and choice. Local decision-making in both the hospital and primary care sectors is encouraged through Area Prescribing Committees (Departmental guidance EL(94)72 "Purchasing and Prescribing").¹³ An example of local guidelines on antibiotic prescribing is attached as Appendix F.

74. Health authority Medical and Pharmaceutical Advisers are available to help doctors analyse their own prescribing patterns and to prescribe most effectively for their patients. GPs receive a quarterly PACT report from the Prescription Pricing Authority (PPA) which details their prescribing patterns. Prescribing advisers can obtain more detailed information on a practice basis electronically from PPA. This performance monitoring information enables professional advisers to monitor the compliance with local policies and intervene, where necessary to change behaviour. Computer software is being continuously updated to improve the availability and accessibility of information from PPA's database. Levels of antibiotic prescribing are frequently included in sets of quality markers in health authority non-fundholder prescribing incentive schemes (decrease in or lower prescribing generally is an indicator of better quality clinical intervention).

Information and support for GPs

75. The Government's objective is to ensure that clinicians have access to the information which will enable them to perform their duties effectively and efficiently, having particular regard to patient safety when prescribing.

76. The British National Formulary (BNF) is an independent publication issued twice yearly to most doctors in the NHS. It provides a comprehensive reference source on all drugs (including strengths, quantities, contra indications and interactions) and therapeutic conditions. An extract from the BNF's general advice on antibiotic prescribing is attached as Appendix G.

77. The Drug and Therapeutics Bulletin (DTB) is an independent publication (published by the Consumers' Association) which the Government distributes free of charge each month to all doctors and pharmacists. It includes rigorous evaluation of treatment regimes and pharmaceutical products, and alerts GPs to the latest developments, putting them into context. Prescribers' Journal and MEREC Bulletins are also funded by the Department of Health.

78. The Government established the National Prescribing Centre (NPC) in April 1996 to promote high quality, cost-effective prescribing through a co-ordinated programme of activities for Health Authorities, Medical and Pharmaceutical Advisers, GPs and managers. The NPC publishes a listing of the various Department/NHS-funded publications which provide information and advice on medicines and prescribing. Attached as Appendix H is an extract which covers advice on antibiotic prescribing over the three year period 1994-96.

79. The Government is funding a research project (PRODIGY) to test the value of computer-aided decision support to both GPs and patients. Computerised decision support may prove to be an effective mechanism to provide suitable guidance adjusted to local conditions to reinforce local policies.

*ANTIBIOTIC PRESCRIBING IN HOSPITALS**Hospital pharmacy input to antibiotic use in the hospital setting*

80. Unlike the community setting, there is currently no central point for the amalgamation of prescribing data in the hospital setting. Antimicrobial agents are estimated to account for 15-20 per cent of drug expenditure in hospitals. It has been suggested that around 25 per cent of all hospital in-patients are prescribed at least one course of antibiotics.

81. Probably to a greater extent than in the community setting, antibiotic policies surround the prescribing and use of antimicrobial agents in hospitals. The majority of prescribing of all medicines is carried out by a

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junior doctor. This holds true for routine prescribing of antimicrobial agents. Expert advice in the shape of a medical microbiologist, infectious diseases physician, or a specialist clinical pharmacist is called upon as needed for non routine prescribing. Access to non routine agents is restricted through the hospital pharmacy.

82. Most hospitals have a ward pharmacy service, where hospital pharmacists visit the wards, each weekday, and scrutinise individual prescription for safety, efficacy and cost effectiveness, advising other health professionals accordingly. During this process they monitor adherence to local prescribing policies, including the antimicrobial policy.

83. Generally a multidisciplinary approach is adopted to the development of local prescribing policies. The antibiotic usually resides in the local hospital formulary. Development of the hospital formulary is co-ordinated by the drug and therapeutics committee through the hospital pharmacy department.

84. Some hospitals have developed preparative services based in the pharmacy department, where the majority of preparation of parental medication is completed under controlled conditions in the pharmacy department. This reduces the risk of medication error, poor preparative technique, and microbial contamination of the product associated with the preparation of parental medication at ward level.

85. Computer aided prescribing is used in some hospitals. Increasingly, this facility is supplemented with "on-line" prescribing information developed or adapted to contain local prescribing policies. Some hospitals in overseas countries have invested in ward based automated drug distribution which further restrict access to medicines. Both of these technological developments will impact on the medicine usage in hospitals.

86. Some hospitals have employed a specialist clinical pharmacist whose role is exclusive to the use of antimicrobial agents. The Hammersmith Hospitals NHS Trust are the leaders in this field. This person works with the medical microbiology and infectious diseases teams. Benefits seen include regular review and monitoring of antimicrobial guidelines, significant decrease in the occurrence of *C. difficile* diarrhoea, improved provision of surgical antibiotic prophylaxis, implementation of evidence based protocols (e.g., once daily administration of gentamicin, appropriate use of highly expensive liposomal amphotericin), appropriate switching from intravenous to oral antimicrobial therapy, and individualised directorate based antibiotic control policy and procedures. Financial savings of £77,000 per annum have been achieved. Future work will consider the relationship between antibiotic resistance and the use of antibiotic specialist pharmaceutical staff.

THE ROLE OF THE MEDICAL DEVICES AGENCY

87. Until 1995, all dressings were regulated under the provisions of the Medicines Act 1988. Under these circumstances, any dressings containing antibiotics were not available over the counter and could only be obtained with a doctor's prescription. In 1995, all dressings, including those containing antibiotics, changed from medicines control to control by the provisions of the Medical Devices Regulations. These Regulations do not allow for any prescription only basis and therefore dressings containing antibiotics can be sold over the counter to the general public.

88. The Medical Devices Agency (MDA) became concerned about this situation in view of the potential for resistance in the presence potentially of suboptimal therapeutic doses of antibiotics. Discussions were held with manufacturers who indicated that there was no cause for concern because there was little market for such dressings. This has in fact not been the case and the MDA have become aware of a number of dressings containing antibiotics coming on to the market.

89. MDA have raised concerns about this subject since 1994 with their Microbiological Advisory Committee and the Committee for the Safety of Medicines and have taken legal advice, with the intention of raising these concerns in Europe. There has been little support however in Europe, chiefly because many antibiotics are already available over the counter in a number of EU countries and there seems to be general acceptance of this practice.

90. MDA also contacted Professor Finch, Professor of Infectious Diseases at Nottingham City Hospital, who has recently set up a working party to look at the issues surrounding the potential availability of antimicrobials over the counter in pharmacies. The report from this group is awaited.

91. In spite of MDA's concerns, it appears that from a legislative point of view there is very little that can be done to address the problem of free availability of antibiotic associated wound dressings. MDA do not yet have sufficient evidence to support taking further action on grounds of public health. However, MDA is keeping a careful watching brief on availability of antibiotic containing dressings and is closely monitoring information relating to the problem of resistance from the topical use of antibiotics.

THE SMAC SUB-GROUP ON ANTIBIOTIC RESISTANT BACTERIA

92. This Sub Group has been set up by the SMAC (paragraph 57) to look at the clinical use of antimicrobial drugs in relation to antimicrobial resistance, under the chairmanship of Dr Diana Walford, director of the PHLS. Its remit is:

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"In the light of the increasing clinical importance of resistance to antimicrobial drugs, to:

- identify the major and emerging problems of antimicrobial resistance in clinical practice;
- identify clinical practices which may predispose to the development of resistance;
- identify practices in antimicrobial use which may help to limit the emergence and spread of antimicrobial resistance;
- identify priorities for changing practice in the use of antimicrobials;
- advise on how such change might most effectively be achieved (with reference to both the public and the professions)."

93. Membership, which is to be expanded, includes representatives from a wide spectrum of clinical interests. The Group held its first meeting in September 1997 and anticipates completion of its first report by mid-1998.

ANTIMICROBIAL RESISTANCE AND THE FOOD CHAIN

Advisory Committee on the Microbiological Safety of Food (ACMSF)

94. In 1996 the ACMSF which advises Health and Agriculture Ministers, set up a Working Group on Microbial Antibiotic Resistance in Relation to Food Safety. The Terms of Reference of the Working Group are: "To assess the risks to humans from antibiotic resistant micro-organisms entering the food chain and to consider the need for any action to protect public health.". The Group agreed that the following broad areas of work should be undertaken:

- assessing the likely scale of the problem of human and animal infections caused by antibiotic resistant micro-organisms in the food chain;
- assessing the role and importance of food and food production as a source of antibiotic resistant micro-organisms for humans; and
- consider the need for any action to protect human health.

95. The Working Group began its programme of work at the end of August 1996 and has considered a substantial amount of written information from a variety of bodies including the pharmaceutical industry, feed producers, medical and veterinary professions and other interested organisations, including consumer and environmental groups, both in the UK, and abroad. The Group is currently taking oral evidence from some of the organisations which responded.

96. To date the Working Group has primarily focused on the veterinary usage of antibiotics as therapeutics and growth promoters although aquaculture has also been considered. The Working Group hopes to begin drafting its report towards the end of the year. This will be submitted to Ministers following endorsement by the Advisory Committee on the Microbiological Safety of Food. The Chairman of ACSMF has provided more details about the ACSMF and the Working Group in a separate Memorandum to the Sub Committee.

Advisory Committee on Dangerous Pathogens (ACDP)

97. The assessment of risks from micro-organisms is fundamental to the work of the Advisory Committee on Dangerous Pathogens. This expert Committee advises Health and Agriculture Ministers, the Health and Safety Commission and the Health and Safety Executive, as required, on all aspects of hazards and risks to workers and others from exposure to pathogens. The ACDP has considerable expertise in microbiological risk assessment (MRA) and published a report on this last year (Microbiological risk assessment: an interim report¹⁴). Antibiotic resistance is one important aspect of MRA. The ACDP is a valued source of advice to government and others on emerging infectious disease threats and keeps abreast of developments in this area, including the increasing concerns about antibiotic resistance.

Advisory Committee on Novel Foods and Processes (ACNFP)

98. In 1994 the ACNFP issued a report on the use of antibiotic resistance markers in genetically modified food organisms (GMO's) and recommended that:

- (a) GMOs which are intended to be consumed live in human foods (such as lactic acid bacteria) should not be permitted to contain antibiotic resistance markers, as alternative markers and procedures for the removal of antibiotic resistance markers have been developed and should be used;
- (b) the use of antibiotic resistance marker genes in foods from genetically modified plants and non-viable genetically modified micro-organisms should be evaluated on a case-by-case basis. The safety evaluation of the food GMOs would include an assessment of the clinical use of the antibiotic, the

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likelihood of transfer of the antibiotic resistance marker gene into, and expression in, gut micro-organisms and the toxicity of the gene product;

- (c) the research community should be reminded of the extent of antibiotic resistance present in micro-organisms and should be made aware of the implications that this has for human health and safety, as well as for veterinary medical practice; and
- (d) researchers developing food GMOs should be encouraged to develop and use alternatives to antibiotic resistance markers and/or methods to jettison those used.

A further report was issued in 1996 which refined the advice given previously and defined in more detail the principles on which the Committee based its safety assessment of antibiotic resistance markers in food or feedingstuff GMOs. The ACNFP acknowledged that many of the GM crops now coming forward for assessment were developed some years ago before alternative marker systems were available and that commercial considerations have required the continued use of proven selection techniques, including the use of antibiotic resistance marker genes. The Committee reiterated the need for such assessments to be made on case-by-case basis and therefore it would not publish prescriptive lists of "acceptable" and "unacceptable" antibiotic resistance marker genes. These reports have been made available to the Sub Committee.

IMMUNISATION POLICY

99. The Health Departments are advised on all matters relating to immunisation by the Joint Committee on Vaccination and Immunisation (JCVI). Its work covers both domestic immunisation policy and immunisation for foreign travel. Immunisation offers protection against an organism regardless of its antimicrobial susceptibility, for example, there is no reason to believe that BCG immunisation offers less protection against drug resistant than against drug sensitive strains, nor that pneumococcal vaccine is less effective against antibiotic resistant strains, as long as the strains are of a type covered by the vaccine.

100. The prevalence of drug resistance in these organisms is not at a level in the UK for modification of the current recommendations for these vaccines to be considered at present. However the situation continues to be monitored, and these and other vaccines would take on increased importance in the prevention and control of infection should antimicrobial resistance increase, either in the UK or abroad.

INFECTION CONTROL MEASURES

Roles and Responsibilities

101. Following two large hospital infection outbreaks in the 1980s, which were the subject of public enquiries, a committee chaired by Sir Donald Acheson published its report "Public Health in England"¹⁵ in 1988. It recommended the establishment of a new medical consultant post to improve the level of activity and expertise in the surveillance, prevention and control of communicable disease and infection. The post of Consultant in Communicable Disease Control (CCDC) was therefore introduced.

102. Health authorities now have at least one CCDC, working with public health medicine colleagues who also contribute to communicable disease surveillance and control. Each Health Authority's (HA) Director of Public Health, takes overall responsibility for the function. The CCDC's responsibilities cover hospitals and the community, and they also have responsibilities within the local authority, which has statutory powers and duties in respect of the control of communicable diseases. Every region has a Regional Epidemiologist (RE) who provides expert support to the CCDC and hospital infection control team, and also acts as a cross boundary co-ordinator. Further guidance on the arrangements for communicable control and the roles of the CCDC and RE was issued in 1991 and updated in 1993 as an Annex to HSG(93)56.¹⁶ In Scotland each health board has a consultant in public health medicine with responsibility for communicable diseases and environmental health.

103. REs have recently carried out a survey of the Communicable Disease Control Functions in England on behalf of Regional Directors of Public Health. This survey is looking at the adequacy of arrangements in Districts and will obtain some information on the links between CCDC's and Trusts. The results of the survey were received in the Department on 17 September and are receiving attention.

Hospital Infection Control Arrangements

104. Activity to prevent, control and treat infection in hospital takes place at many different levels. Many routine practices to prevent infection relevant to the prevention of spread of antimicrobial resistant organisms are carried out as part of the day to day work of doctors, nurses and other professional health care staff. Staff are backed by the usual range of core services such as laboratories, sterile supply, laundry, etc. Although infection control services are largely undertaken by medical and nursing staff with the relevant specialist

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expertise, managerial interest and input at a strategic level is essential. The Chief Executive of every hospital is responsible for ensuring that there are effective arrangements for infection control in place and subject to regular review.

105. In 1988 a joint working group was set up by the then Department of Health and Social Security and the Public Health Laboratory Services (PHLS) to produce advice on the control of infection in hospitals. The working group's report recommended the appointment of specialist infection control doctors and nurses in all acute hospitals and the establishment of Infection Control Committees. In 1992 a new joint working group was established to revise and expand the 1988 report. New guidance was produced and this was issued by the Department in March 1995 under cover of HSG(95)10.¹⁷ This guidance strengthened previous recommendations and included new advice on improving surveillance of HAI. In 1996 a working group was set up in Scotland to review the control of infection in hospitals with a view to issuing guidance by the end of 1997.

106. The working group's main recommendations were that:

- every hospital should have a specialist Infection Control Team (ICT) and a Hospital Infection Control Committee (HICC) to cover all facilities;
- the ICT should have primary responsibility for, and report to the Chief Executive on, surveillance, prevention and control of infection in the hospital;
- all general hospitals need to have sufficient isolation facilities available, either in suitable side rooms on general wards or in a separate isolation ward, or both;
- there should be an effective infection control programme with defined objectives in place within hospitals and it should be reviewed regularly;
- routine surveillance of HAI, including those not associated with outbreaks, should be undertaken;
- commissioners of health care should include enhanced surveillance, prevention and control in their contractual arrangements;
- the Health Authority's CCDC should liaise regularly with the ICT, be a member of the HICC, advise commissioners on their contractual requirements and be very closely involved in the management of any hospital outbreak;
- the hospital should call upon expert advice, for example from the PHLS, whenever necessary.

Health and Safety Executive

107. The Health and Safety Executive (HSE) is responsible for enforcing the provisions of the Health and Safety at Work, etc., Act 1974 (HSWA). The HSWA regulates all work (except domestic service) and places general duties on employers, employees and the self-employed. Section 3 of the Health and Safety at Work, etc., Act 1974 (HSWA) requires employers to safeguard the health and safety of people other than their employees who may be affected by work activities (including, for example, patients and members of the public). The HSWA and secondary legislation, such as the Management of Health and Safety at Work (MHSW) and Control of Substances Hazardous to Health (COSHH) Regulations, apply to the control of infection in hospitals and nursing homes.

108. The Health and Safety Commission and HSE, in conjunction with Health Departments and other agencies, have issued guidance on the prevention of infection with regard to, for example, the control of clinical waste, Legionnaires' disease and the safety of staff in post-mortem rooms and laboratories. Laboratory safety is based on series of containment levels which are linked to the classification of pathogens according to their ability to infect. As part of this classification the availability of effective prophylaxis (e.g., antibiotics or vaccines) is considered.

109. Effective control of infection in hospital protects both staff and patients, and relies on the proper application of systems of work such as the Control of Infection procedures detailed in the 1995 Department of Health/PHLS guidance (see paragraph 105). HSE Inspectors consider issues relating to infection control and the availability of ICT's as part of their normal preventive inspection of health and safety management in hospitals.

110. As regards the prescription and use of antibiotic, it has long been agreed that HSE will not use s.3 of HSWA to regulate matters concerned with clinical decisions about care of patients, for which other agencies and professional bodies are responsible. Therefore it would not be appropriate for HSE to act in areas relating to clinical decisions on the use of antibiotics (prescribing policies) or on the use of particular medicines. These are properly regulated under specific legislation by the General Medical Council or the Medicines Control Agency.

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DEPARTMENT OF HEALTH GUIDANCE AND RECENT ACTION

Priorities and Planning Guidance

111. The 1997–98 Priorities and Planning Guidance⁽¹⁸⁾ (PPG) for the NHS makes it clear that HAs should have in place appropriate multi-disciplinary arrangements for infection and communicable disease control. It also states that HAs should satisfy themselves that their providers have appropriate arrangements for infection and communicable disease control, based on expert advice. The 1998–99 PPG⁽¹⁹⁾, just issued, makes it clear that the obligations which HAs have for communicable disease control in relation to the protection of the public health must be fulfilled. The delivery of these objectives is being monitored and reviewed through the performance management process. In February 1997 EL(97)13⁽²⁰⁾ was issued to the NHS to remind HAs and Trusts of their responsibilities for ensuring that appropriate arrangements for communicable disease surveillance and control are in place.

Contract for the Provision of National Support Services for NHS Activity in the Control of Communicable Disease

112. In November 1995, a service level agreement was established between the NHS Executive and the PHLS for the PHLS to provide a regional epidemiology service to Regional Directors of Public Health and other relevant professionals concerned with the prevention and control of infectious disease. The agreement took effect from 1 April 1996 and is intended to remain in force for three years. It will be reviewed before the end of the three year period and may be renewed thereafter.

113. The main elements of the service provided in each region consist of monitoring arrangements for the control of communicable diseases and infection, service development, surveillance, advice and operational support, training and professional development, and audit of communicable disease control and services.”

Nosocomial Infection National Surveillance Scheme

114. The Department has worked closely with the PHLS to fund and establish within PHLS a Nosocomial Infection National Surveillance Scheme (NINSS). A multidisciplinary team at the PHLS has developed and piloted standardised methods for estimating rates and risk of hospital-acquired bacteraemia and surgical site infection. The aim is to produce consistent, anonymised data on HAI to enable hospitals to compare their infection rates with others and review the efficacy of their infection control practices. Extension of the Scheme to cover surveillance of other infections, probably lower respiratory and urinary tract infections, is being considered. Ninety hospitals in England have participated in the NINSS programme during its first year. It is hoped that all acute hospitals will join the Scheme and that in future methodology suitable for surveillance in long-stay hospitals will also be developed. A working party has been set up in Scotland towards achieving a national surveillance system for hospital infection.

MRSA

115. In September 1994 the Department issued guidance under cover of EL(94)74⁽²¹⁾ entitled “Improving the Effectiveness of the NHS”. It commended to the NHS previously published guidance on the control of MRSA in hospitals. This guidance was produced by two of the interested professional organisations—The Hospital Infection Society and the British Society for Antimicrobial Chemotherapy. The Department has been represented on a working group which has been revising these guidelines with added representation from the Infection Control Nurses Association. The new guidelines are expected to be published in the next few months.

Tuberculosis

116. Detailed guidance on tuberculosis control from the Interdepartmental Working Group on Tuberculosis was published in June 1996 and widely circulated under cover of EL(96)51.⁽²¹⁾ The report “*The prevention and control of tuberculosis at local level*” which was included in the guidance clearly stated “the prevention of the emergence of drug resistant tuberculosis” as one of the aims of national policy, and both that report, and the report “*Tuberculosis and Homeless People*” (also included in the guidance) made recommendation concerning measures to achieve this. The recommendations for local control contain infection control guidance equally applicable to preventing the spread of drug sensitive and drug resistant organisms.

117. In response to requests from the field the Department is preparing guidance to supplement that already issued, giving more detailed advice on prevention and control of the transmission of tuberculosis which is drug resistant or associated with HIV infection. These are expected to be published during 1997.

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Infection Control Clinical Guidelines

118. The Department has recently invited tenders for the production of new National Hospital Infection Control Clinical Guidelines concentrating on the major issues associated with HAI. These will serve as a model for the review and development of local infection control policies and procedures.

The Clinical Audit of Hospital Infection Control Activity in England and Wales

119. This project was set up by the PHLS to audit activities designed to control HAI in 19 hospitals. Funded by the Department, it was carried out over a three year period by a multi-disciplinary team. The project findings have recently been published in the report *Hospital-Acquired Infection: Surveillance, Policies, and Practice*.²²

120. This was the first major study in England and Wales to estimate the incidence of certain types of HAI and some of the risk factors involved. The infections studied included those of the urinary tract, respiratory tract, and bloodstream, in patients receiving treatment in general wards and intensive care units. Device usage relating to the infections surveyed was also monitored because of the link between devices and HAI.

RESEARCH

121. The Department's Microbiological Food Safety (MFS) Surveillance and Research programme has funded three projects relevant to the issue of microbial antibiotic resistance. The Department is currently funding the PHLS's Laboratory of Enteric Pathogens (LEP) to examine the molecular epidemiology of multiresistant *Salmonella typhimurium* DT104 in England and Wales. This two year project, which began in April 1996, will assess whether further differentiation of this organism can be achieved to assist epidemiological investigations and outbreak control. In addition, the work will further our understanding of the genetic mechanisms responsible for resistance in this emerging foodborne pathogen.

122. Exeter Public Health Laboratory have been funded by the Department to examine the tolerance and survival of salmonellas, particularly *S. typhimurium* DT104, in relation to heat, acid and commonly used preservatives. The Department has also funded Southampton Public Health Laboratory to examine the prevalence of quinolone resistance in isolates of *Campylobacter* from gastrointestinal infections and to identify risk factors associated with these infections.

123. The Department also funds a number of projects relating to antimicrobials, rapid laboratory diagnosis and hospital acquired infection, both through the Central R&D programme and through the NHS.

124. Funding through the Medical Research Council for research relating to infections and antimicrobial agents amounted to £2,169K in 1995-96. This covers grant (indirect) support and direct support for research in MRC establishments. While the proportion of this directly related to antimicrobial resistance is relatively small, it is an area in which the Research Boards are showing particular interest.

125. Research is also being undertaken at the Centre for Applied Microbiology and Research (CAMR). Details of this are given in paragraph 129.

Vaccine Development

126. The Department's Policy Research Programme is currently funding two Phase 2 trials of meningococcal and pneumococcal vaccines. Such research is not specifically targeted at antibiotic resistant organisms.

THE ROLE OF OTHER BODIES

The Public Health Laboratory Service

127. The Public Health Laboratory Service (PHLS) protects the population from infection by maintaining a national capability of the highest quality for the detection, diagnosis, surveillance, prevention and control of infections and communicable diseases. This includes monitoring antimicrobial resistance and hospital acquired infections (HAIs) which are recognised as being amongst the priority areas for the PHLS. The PHLS addresses these problems through the co-ordinated activities of its network of microbiology laboratories, its reference laboratories as well as its research and development programme.

The National Institute for Biological Standards and Control (NIBSC)

128. Most antibiotics are not now classed as "biologicals" and therefore fall outside the remit of NIBSC. The NIBSC provides international reference materials on behalf of the World Health Organisation for those antibiotics that are the subject of microbiological assay (now rare for new agents and being replaced for some

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established antibiotics) and for bacterial vaccines and related materials. NIBSC is also closely involved in the licensing and control of bacterial vaccines through assessment procedures and batch release (this involvement is at both national and European levels), and in the control and standardisation of new vaccines (e.g., meningitis, haemophilus, pneumococcal). NIBSC conducts research into the nature/quality and safety/efficacy of bacterial vaccines. NIBSC is carrying out a WHO funded project on malaria vaccine and on the requirements of synthetic peptide vaccines.

Centre for Applied Microbiology and Research (CAMR)

129. The Department of Health funds a programme of research at CAMR, amounting to over £4 million in total, aimed at a range of public health needs, including vaccine research and development, and studies of the pathogenesis of organisms which, among other outputs, will lead to insights into strategies for the development of new therapeutics. Examples of current work are:

- a project to determine whether *S. typhimurium* DT104 is invasive in poultry and whether invasiveness correlates to extreme environments and/or the acquisition of antibiotic resistance;
- testing patient samples, as part of the Tripartite Vaccine Assessment Programme (with NIBSC and CDSC, PHLS), to provide essential information for the development of effective vaccines in the UK;
- a research programme aimed at developing improved ways of delivering vaccines so that they are both easier to administer, i.e., by mouth, and more effective;
- projects to develop improved vaccines against *Neisseria meningitidis* (a causative agent of meningitis) and *Streptococcus pneumonia* (a cause of a wide range of diseases including meningitis);
- a project aimed at developing improved systems for the production of influenza vaccine.

CAMR is directed by its Board, the Microbiological Research Authority, a Special Health Authority at Porton Down, Salisbury. CAMR's special resources include containment facilities for the handling of the most dangerous pathogens and biological toxins. CAMR also have considerable commercial interests and manufacture a number of therapeutic products. A separate memorandum of evidence from CAMR outlining areas where it believes it can make additional contributions in the area of antibiotic resistance has been forwarded to the Sub Committee.

THE PHARMACEUTICAL INDUSTRY

130. The Association of the British Pharmaceutical Industry (ABPI) is submitting its own evidence to the Sub Committee.

THE INTERNATIONAL PERSPECTIVE

International Dimension

131. Several overlapping initiatives have developed recently involving international collaboration over the surveillance of antimicrobial resistance, in recognition of its importance as an emerging problem in communicable disease control.

The European Union

132. Within the Public Health Framework run by DGV, a Community action programme dealing with surveillance and the promotion of preventative measures in relation to HIV/other communicable diseases has been up and running since 1996. Priority areas include antimicrobial resistance. One project within the programme, on the surveillance of tuberculosis, has recently been extended to include surveillance of drug resistance. A proposal for a more comprehensive European Antimicrobial Resistance surveillance system has recently been submitted for funding.

133. The European Union is also currently in the process of negotiating a Community action programme, which will establish a network for the epidemiological surveillance and control of communicable diseases. The planned purpose of this network will be to put national centres for the surveillance of communicable diseases in communication with each other in order to collect, analyse and make available health data concerning the risk factors and patterns of spread of certain communicable diseases where European collaboration will give added value to enable the appropriate preventative measures and counter-measures to be taken. It is hoped that the network will be operational by mid 1998.

134. The proposed programme of work contains an indicative list of communicable diseases gradually to be covered by the network:

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- diseases preventable by vaccination;
- sexually transmitted diseases;
- viral hepatitis;
- food and water borne diseases;
- nosocomial infections;
- other diseases transmissible by non-conventional agents (including CJD);
- diseases covered by the international health regulations (yellow fever, cholera and plague);
- other diseases (rabies, typhus fever, viral haemorrhagic fevers, malaria and any other as yet unclassified serious epidemic disease).

135. The European Commission has also recently commissioned a survey of current surveillance and control measures for hospital acquired infection within the Member States.

136. Research into immunology and trans-disease vaccinology forms an important part of the ongoing Community-wide "Fourth Framework Programme of Research and Technological Development". This programme was established in 1994 and will expire in 1998. In 1996 the budget for the Biotechnology component of the Fourth Framework programme was 139 million ECUs (£93 million).

137. The European Union's 5th Framework, as currently drafted, will have a key action on the control of infectious diseases. The current wording is as follows:

Close attention is to be paid to new and improved strategies to control infectious diseases, directed at treatment and prevention and based on studies on pathogenesis, emergence of resistance and immunological control.

The EU will therefore be supporting research and development in relevant areas.

The EU-US Task Force

138. Under the new Transatlantic agenda, a joint EU-US Task Force on communicable diseases was established in 1996. One Working Group of the Task Force, which is working on issues relating to surveillance and response, identified antimicrobial susceptibility as a priority for further work, and discussions are under way on ways of stepping up joint involvement of the EU-US in monitoring antimicrobial susceptibility, both in their respective regions and globally.

The World Health Organisation (WHO)

139. WHO has set as its long-term goals:

- to encourage policies and practices that will ensure better infection control and patient care at local level;
- to prolong the useful life of available antimicrobials;
- to support rational selection of regional essential drug lists;
- to detect and contain the emergence of new and major multidrug resistant bacteria;
- to support those involved in antimicrobial drug research, development and advocacy.

The WHO Antimicrobial Resistance Network (WHONET)

140. In addition to its already established work on antimicrobial susceptibility surveillance, the WHO is establishing a global network of laboratories to monitor antimicrobial resistance using reliable methods for testing for resistance. WHO is also developing a global database. Software has been made available to participating laboratories to input antibiotic resistance data which will be used to identify antimicrobial resistance problems of local, regional and global priority, seek consensus on how to tackle these problems, and initiate and co-ordinate appropriate control and containment measures.

141. Fifty laboratories will provide standardised, quantitative antimicrobial susceptibility testing data to WHO by the end of 1997. The Network will be expanded to 60 per cent of WHO Member States in 1998 and to 80 per cent in 1999. Fundamental to the network is development of standard methods and quality control in laboratories. Training and training manuals, software and other materials have been made available.

Research

142. WHO also carries out its own health research into these types of bacteria and stimulates research in the international health community in liaison with the world scientific community, other international and national agencies, the WHO Advisory Committee on Health Research and WHO's expert committees.

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Drug Development

143. The Joint WHO/IFPMA meeting in November 1996 resulted in an agreement on a framework for future collaborative efforts between WHO and the pharmaceutical industry to contain the spread of antibiotic resistant bacteria, with the aim of improving opportunity for successful, cost-effective treatment for infections and to encourage research and development of new antibiotics.

CONCLUSIONS

144. The potential threat to public health in the UK posed by antibiotic resistant human pathogens is recognised. The threat has arisen following more than 50 years of antibiotic usage and is particularly related to a dwindling supply of new antibiotics and to a hospital population that is increasingly susceptible to infection. However, the situation in the UK is considerably less severe than in many other countries and is amenable to control and improvement. Several initiatives have been undertaken or are underway in the UK aimed at preventing the further emergence and spread of antimicrobial resistant organisms, including:

- enhanced surveillance in several areas;
- a review of the clinical use of antimicrobials;
- a review of antimicrobials in the food chain;
- infection control measures;
- international collaboration;
- promotion of research in the field, and into the development of new antimicrobial agents and vaccines.

145. Taken together and with support from healthcare professionals from expert groups and professional bodies these measures provide an opportunity to limit the most serious consequences of multiple antibiotic resistance occurring in the country.

GLOSSARY

ABPI	Association of the British Pharmaceutical Industry
ACDP	Advisory Committee on Dangerous Pathogens
ACMSF	Advisory Committee on the Microbiological Safety of Food
ACNFP	Advisory Committee on Novel Foods and Processes
C. DIFFICILE	Clostridium Difficile
CAMR	Centre for Applied Microbiology and Research
CCDC	Consultant in Communicable Disease Control
CDSC	Communicable Disease Surveillance Centre
CJD	Creutzfeldt-jakob Disease
CMO	Chief Medical Officer
COSHH	Control of Substances Hazardous to Work
E. COLI	Escherichia coli
GMO	Genetically Modified Food Organisms
H. PLYLORI	Helicobacter Pylori
HAI	Hospital Acquired Infection
HICC	Hospital Infection Control Committee
HSE	Health and Safety Executive
HSWA	Health and Safety at Work Act
ICT	Infection Control Team
JCVI	Joint Committee on Vaccination and Immunisation
MDA	Medical Devices Agency

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MDR-TB	Multidrug Resistant Tuberculosis
MRSA	Methicillin-resistant <i>Staphylococcus Aureus</i>
MYCOBNET	Mycobacterial Resistance Network
NIBSC	National Institute for Biological Standards and Control
NINSS	Nosocomial Infection National Surveillance Scheme
PHLS	Public Health Laboratory Service
PPG	Priorities and Planning Guidance
RE	Regional Epidemiologist
S. AUREUS	<i>Staphylococcus Aureus</i>
VRE	Vancomycin Resistant Enterococci
WHO	World Health Organization
WHONET	World Health Organisation Resistance Network

REFERENCES

1. Emerging infections: Microbial threats to health in the United States.
2. Department of Health. On the State of the Public Health, 1995: The Annual Report of the Chief Medical Officer of the Department of Health 1995. HMSO. London. 1996.
3. Department of Health. On the State of the Public Health, 1996: The Annual Report of the Chief Medical Officer of the Department of Health 1995. HMSO. London. 1997.
4. WHO Scientific Working Group on Monitoring and Management of Bacterial Resistance to Antimicrobial Agents. WHO/CDS/BVI/95.7, 1995.
5. Resistance to methicillin and other antibiotics in isolates of *Staphylococcus aureus* from blood and cerebrospinal fluid, England and Wales 1989–95. Speller DCE, Johnson AP, James D *et al.* Lancet 1997; 350: 323–25.
6. Reduced susceptibility of *Staphylococcus aureus* to Vancomycin—Japan, 1996. MMWR 1997; 46: 624–6.
7. *Staphylococcus aureus* with reduced susceptibility to vancomycin—United States, 1997. MMWR 1997; 46: 765–6.
8. Resistance to Penicillin (PHLS).
9. Prevalence of antibiotic resistance in pneumococci. Wilson P, Lewis D, BMJ 1996; 313: 819–20 Allen KD, Anson JJ, BMJ; 313: 820.
10. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. Avason VA, Kristinsson KG, Sigurdson JA *et al.* BMJ, 1996; 313: 387–91.
11. Tuberculosis—Drug Sensitivity.
12. British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals. Lancet 349: (9058):1086–1092. 1997.
13. Department of Health: EL (94)72 Purchasing and Prescribing.
14. Public Health in England: The Report of the Committee of Inquiry Into The Future Development of the Public Health Function. HMSO London 1988.
15. Department of Health Health Service Guidelines: HSG(93)56 Public Health: responsibilities of the NHS and the roles of others.
16. Department of Health/PHLS Health Service Guidelines: HSG(95)10 Hospital Infection Control—Guidance on the control of infection in hospitals.
17. NHS Executive: Priorities and Planning Guidance for the NHS 1997–98.
18. NHS Executive: Priorities and Planning Guidance for the NHS 1998–99.
19. NHS Executive Executive Letter: EL(97)13 Public Health: Responsibilities of the NHS.
20. NHS Executive Executive Letter: EL(94)74 Improving the effectiveness of the NHS.

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21. NHS Executive Executive Letter: EL(96)51 two Reports of the Interdepartmental Working Group on Tuberculosis.

22. Public Health Laboratory Service: Hospital Acquired Infection: Surveillance policies and practice—A report of a study of the control of hospital acquired infection in 19 hospitals in England and Wales.

Examination of witnesses

TESSA JOWELL, a Member of the House of Commons, Minister for Public Health, was examined; and SIR KENNETH CALMAN, Chief Medical Officer, DR GRAHAM WINYARD, Deputy Chief Medical Officer and Medical Director of the NHS, MRS GILL STEPHENS, Assistant Chief Nursing Officer, and DR MARY COOKE, Senior Medical Officer, Department of Health, were called in and examined.

Chairman

753. Minister, thank you for coming along and giving your time to this investigation.

(Tessa Jowell) Thank you very much indeed for the invitation to give evidence today. The Government very much welcomes the opportunity to contribute to your enquiry, which, as you are all aware, has generated considerable interest and we believe helped to stimulate much needed debate about the growing national and indeed international problem of antimicrobial resistance. The weight of written evidence that you have received and what has been said to you by many experts in your wide-ranging public sessions is very clear evidence of that concern. We must acknowledge, of course, the major contribution that antimicrobial agents have made both to our health and to our longevity in the twentieth century and their continued availability and efficacy is essential. Without them many of the major technological advances in treatment simply could not be used. While the problem of resistance that we are experiencing in the United Kingdom is very real, these are not of the severity seen in a number of other countries. Our relative success, we believe, is due to the absence of over-the-counter and inferior quality antibiotics, to good laboratory and infection control services and to a relatively restrained approach to prescribing. We see this as an issue which is one of concern, but one which needs to be held in proper proportion in terms of its overall scale. Although antimicrobial resistance was highlighted in the CMO's reports for both 1995 and 1996 as a key area of future work, its importance has, of course, been recognised by the Department for very much longer. While there are no grounds for complacency at all, much has already been achieved in monitoring, preventing and controlling drug resistance. For instance, prescribing policies and local and national formulae have been in use for many years. While these were partly driven by the need to contain expenditure on drugs, they have also attempted to provide for rational antibiotic prescribing. I think that we can claim some success. The use of antimicrobials in the United Kingdom is relatively modest compared with other countries. The second area relates to our assessment and action in relation to the use of multiple drug therapy for tuberculosis to prevent the emergence of drug resistance and this risk was recognised very early, and

the acceptance of standard protocols for treatment has almost certainly kept resistance levels in the United Kingdom at the low levels that we see now. However, TB does raise an issue that perhaps will be discussed later on, and that is the international dimension of the problem of antimicrobial resistance and the likely impact on the United Kingdom of the importation of drug resistant strains from abroad. On MRSA also there is much that we can be proud of, although it does remain a problem. Because we have high quality infection control services and relatively constrained antibiotic usage here, compared with many other countries, we are still in a good position to keep up our efforts to keep it under control. In many countries no such effort is made, although there are other examples where we believe that we can learn from other countries and we intend to do so. We believe our surveillance of the organism to be the best in the world, although we have plans to improve it even further. Very few other countries have national data on it, but the information that there is suggests that MRSA prevalence here is much lower than in most countries in Europe and elsewhere. For instance, the average prevalence in 1990 to 1995 was said to be 30 per cent in France and 60 per cent in Japan, compared with only eight per cent here. The excellent clinical guidelines produced by the BSAC and the Hospital Infection Society have also been a great help. The Department commended them to the NHS several years ago and has been closely involved in the current update which we hope will be ready for publication very soon. In 1995 the Department of Health also issued guidance on the care of people with MRSA in the community. That is a matter referred to by the CMO in his report. This was very well received by professionals involved in caring both for people in their own homes and in residential nursing homes. That guidance has been widely disseminated. However, there is now a general acceptance that a much more pro-active approach to antimicrobial resistance is needed, and this is not for the Department of Health alone. There can be no quick, short-term solution that will guarantee that we resolve the problem forever, as I am assured your enquiry has made clear. We need to think in terms of the legacy we are leaving for future generations. It is a complex issue, needing the attention and cooperation of a very wide range of organisations and individuals, such as those that have already given evidence to you. We look

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forward in government to receiving your report and recommendations which, I have no doubt, will, in the future, be seen as a major contribution to debate and future actions on this important subject.

754. Does any other member of your team wish to make any opening comments?

(Tessa Jowell) They will have plenty to say as the session continues, Lord Soulsby!

755. You referred in your opening comments to the 1995 report of the Chief Medical Officer, where it was identified that antimicrobial resistance is a key area for further work and the CMO reported some action in 1996. You have done a mapping exercise. We would like to know what progress has been made towards mounting a strategic attack on the problem as has been done in Denmark. What are your key objectives and what are the next moves?

(Tessa Jowell) This is a key question because it is very important to see the whole issue of antimicrobial resistance in the context of a wide-ranging strategy. A wide-ranging number of approaches and interventions need to be in place in order that we apply the knowledge of infection control and proper surveillance across the range that is required. Perhaps I can very quickly set out what are the main elements of the strategic approach that we take and I have no doubt that the Chief Medical Officer, who has overall responsibility for this across government, will want to make a contribution. Perhaps we can look, first of all, at the protection of human health. This involves improvement in the surveillance conducted both by the Department of Health and by the Public Health Laboratory Service, of which I know you will have heard a lot. Secondly, there is the issue of changing and constantly informing and re-informing clinical practice. Work in that area is being undertaken by the Standing Medical Advisory Committee. Thirdly, there are specific issues in relation to the delivery of health care and the running of the health service, issues like infection control which the Chief Medical Officer's wider project touches on, as does his recent work assessing the competence and capacity of the public health function at a local level. Then there is the fourth key area which is public information, both about the risks that are posed by this and very much in tune with our approach to public health, making sure that members of the public, when they go to their GP, have information about what they can do. That means, as we will come on to later, not necessarily asking for or demanding a prescription for antibiotics every time they see their doctor. The fifth area in relation to the protection of human health is also international collaboration. I referred in my opening remarks to the importance of our being able to learn from the innovations in other countries and to draw on the experience in this area of the World Health Organization and the EU, the joint EU/US government initiatives, and you will be aware that there is currently before the Council of Ministers, the Health Council, a proposal for a European-wide network for communication and surveillance in relation to infectious diseases. Sixthly, in relation to the protection of human health there is the issue about the

competence of existing legislation and the need, which I am sure you know we recognise, for new legislation to update existing legislation for the control of infection. Finally, there is the important area of new developments in relation to vaccine, basic science, the role of the pharmaceutical industry and innovations as a result of new drugs.

Perhaps I can touch briefly on animal and plant concerns. First of all, the clinical practice of vets, which I know is a matter that has been of concern to you, the use of growth promotion agents in relation both to animals and plants, the importance of improved surveillance which we see as an important function for our new Food Standards Agency, the White Paper setting out proposals which was published two weeks ago, proper attention to the food chain and the control of microbiological agents in that context which the Advisory Committee on the Microbiological Safety of Food is currently examining. There are important international issues and there are issues about the competence and scope of existing legislation, both at an EU and a domestic level. We see the scope of this strategy as being extremely wide-ranging and crossing at least two departments of government, MAFF and the Department of Health. I hope that that is useful background to the further information about the mapping exercise to which you referred, which was undertaken by a small project team during 1997, and which really confirmed the breadth of concern, and the breadth of potential involvement of both government and non-government agencies with an interest in antimicrobial resistance. The report outlined the main characteristics of a generally strategic approach to the problem and suggested a number of particular issues to be considered within an overall framework. As you will be aware we listed some of the key elements of the strategy in our evidence to you which I would be happy to discuss further in questions if you wish. The Standing Medical Advisory Committee are acting as the umbrella under which a working group was established in order to examine further the clinical importance of resistance to antimicrobial drugs, in the light of major and emerging problems of antimicrobial resistance. They were also charged with identifying clinical practices which may predispose the development of resistance, and practices in antimicrobial use which may help to limit the development and spread of resistance, and to advise on how such change might most effectively be achieved for both the professional and the public. Again, that is a major and a wide-ranging remit. The draft report is expected to be considered by the committee at its April meeting and we regard the work of this group as an essential prerequisite to the development of a truly strategic approach in the clinical area. As far as preventing the spread of microbial pathogens, including drug resistance, is concerned, work on revising the current guidelines for the prevention and control of MRSA and work on more detailed guidance on prevention of transmission of drug resistant tuberculosis has progressed, and we have put out to tender and now commissioned detailed clinical guidelines on infection control which will help set national standards and we hope ensure national

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consistency. On the research front, just over a week ago the MRC held a preliminary brain-storming session which included Department of Health representatives to identify and discuss the research needs in this area, and how they might be taken forward. All these areas, and of course the report and recommendations of your Lordships' enquiry, will help us further develop the strategy for the future. I mentioned in my opening remarks that a fully comprehensive strategy would have to involve departments and agencies beyond the Department of Health and we will be considering how this might be best achieved in the future. Finally, in the light of your interest in the experience in Denmark, we are very interested in what has been achieved there. We understand that their approach has involved a three-pronged strategy, involving chief executives, tight national prescribing policies for antimicrobials and strict adherence to infection control procedures. We are studying published material and plan to visit to see at first hand what has been achieved there and what lessons might be applied for the benefit of patients in the United Kingdom.

Lord Perry of Walton

756. We were impressed when we were in America, in fact, we were frightened by the information that we received about the development of resistance. Many of our witnesses have said that the progress of drug resistance amongst all micro-organisms is slow but inexorable. We all agree with your own assessment that we are better off in the United Kingdom than many other countries. On the other hand, because of the fact that it is inexorable, do you agree that it is very urgent that we should take a lot of these steps, many of which will be very expensive, and that the Government should be prepared to meet the cost of expenditure because the situation is urgent?

(*Tessa Jowell*) With your permission, Chairman, I would like to ask the Chief Medical Officer to comment on that in the light of his assessment. I am glad that you acknowledge that in the United Kingdom we are at the leading edge, and I would reiterate what I said in my opening remarks, that we do recognise the problem, we do recognise the extent to which this can be a consequence of progress. We do need to keep ahead of it, but it is also a matter which needs to be kept in proper proportion and under control. Our determined efforts are to construct a strategy that enables us to do that.

(*Sir Kenneth Calman*) My Lord Chairman, I agree entirely that this is a very important area of concern to public health. As the Minister has said, we need to get this into perspective too. Antibiotics are extremely valuable; they are life-saving. We have evidence, not only in this country, but elsewhere of this emerging problem. Its extent varies from country to country. We happen to be reasonably well ahead, but, as you rightly say, that makes it all the more important that we have, first of all, a cohesive strategy, a strategy that crosses Government, as the Minister has said, but also, secondly, that that is linked to research, to clinical

practice, to industry and other agencies and the international community in health and public health research. As far as the funding for that is concerned, it is the Minister's responsibility to respond to that. I am under no illusions at all, and that was why I raised it in the annual report, that this is something that is likely to come on us unless we take steps at this stage to control it. The objectives we would have might be three. Firstly, to reduce the prevalence of micro-organisms resistant to current drugs. The experience in Denmark suggests that that might be possible to do. The second is that as new drugs are introduced we develop with the specialties, clinical practice and guidelines which reduce the possibility of resistance developing, although resistance, I suspect, is inevitable for most of the antibacterial agents. The third thing is to have in place in the hospital and in the community infection control policies which would limit the spread and control it. That is about clinical practice, managing the service, and having a monitoring and surveillance system that allows us to pick up things at the earliest possible stage. In summary, I agree with your comments, indeed that is why we are here, and I am delighted your Committee has taken this on.

Chairman

757. Minister, you and the Chief Medical Officer referred to the international situation. There are two international situations. One is local, the European Union situation, and there is the broader international situation. Some people have said that until we get our European Union act in order we are not going to make a lot of progress internationally. I am sure you are well aware that there are certain countries of the European Union where antibiotics are for sale freely over the counter. Have you any comment on what is being done in Brussels, for example, with respect to this?

(*Sir Kenneth Calman*) In terms of the broader international sphere, the World Health Organization, indeed in its Executive Board meeting last week, passed another resolution about the importance of antibiotics, again signalling the need for countries to cooperate in this. I think it is fair to say that the experience of Denmark suggests that individual countries can do something. The second issue is about the EU. There are several task forces and activities going on now which in some sense have been led by the United Kingdom, particularly in the last Presidency, and indeed they will be taken forward in this Presidency, where there are different prescribing habits and availability across the countries in the EU. I would have thought that is an area that encourages the development of resistance in some places, and that is an issue which I have raised with the European Chief Medical Officers, for example, and during the Presidency, in March of this year, it is an issue which will certainly come up again in terms of antibiotic prescribing. It is partly related to treating illness, but also it is about postgraduate education and how doctors think about practising and it has come up in that context about medical education as well as in the context of managing disease.

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Baroness Masham of Ilton

758. The world is very small with air travel and it is a global problem. The Minister said that her Department was in touch with other agencies. With regard to air travel, what do you think about screening of at-risk people because there have been some cases of doctors coming in with HIV and TB?

(*Sir Kenneth Calman*) This is an issue which is covered under port health regulations and it is an issue which is of particular concern. It happens in other countries too where people may come in, particularly if they are being admitted to hospital, to check that they do not have an antibiotic resistance problem. The very specific issues of tuberculosis and drug resistance and HIV people who might have tuberculosis are clearly well recognised by people at the port health authorities in relation to those who are being admitted. There is a real concern that that particular group of people are handled in a way which, first of all, improves their chances of survival, but reduces the possibility of transmission of any drug resistant infection to anyone else in the vicinity. We will perhaps discuss this later, but in terms of infection control generally, I think hospitals in the community are very well aware that that is a very real possibility.

Baroness Platt of Writtle

759. Minister, you touched on the question of the imprudent use of antibiotics in general practice for symptoms of self-limiting infections such as coughs, or even colds, where there is no benefit at all. This obviously costs money and encourages resistance. The Royal College of General Practitioners told us that if practice is to change, it must be supported by public consensus, which you touched on too, and not just driven by doctors. Are you prepared to lead a consensus-building campaign in this area?

(*Tessa Jowell*) It is clear from the evidence that you have received that there is a lot of support for consensus building, aimed both at doctors, other health professionals and the public. We recognise that this is a difficult area, but one that we and professional organisations and others concerned have recognised and are beginning to address. To go back to what I said in my opening remarks, there is an expectation of patients for a consultation with their GP to conclude with the provision of a prescription and that can be difficult for a busy and hard-pressed doctor to resist. I think it is accepted that we need to look at ways and means of both public and professional education around this issue. Some limited work has already been done. For instance, there is the Department information leaflet on flu which promoted the message that antibiotics will not help unless the flu led to another illness, and the Department welcomed the BMA's *Antibiotics—Not a Miracle Cure* initiative as part of its Doctor/Patient Partnership campaign. This aimed to raise awareness both that most infections will get better without the need for antibiotics, and the downside which you imply of unnecessary antibiotic usage. We have already, therefore, made a start at looking at this whole area in detail. The working group of the Department's Standing Medical Advisory

Committee is looking at issues around clinical prescribing of antimicrobial drugs, particularly as regards best practice. In addition to representation of Royal Colleges, other standing advisory committees and junior doctors, PHLS and veterinary medicine, there is consumer representation and the sub-committee is looking very much at how changes in practice and expectations might best be achieved for both professionals and the public. That committee aims to produce its report in the summer. Education of this kind can be expensive and we need to balance activity against potential savings. As with so much of our health education activity, I am very concerned that we ensure that we assess the cost-effectiveness of the leaflet campaigns and public education campaigns. We also need to consider very carefully how to ensure that parents do take their children to the doctor and take them urgently in situations where immediate antibiotics may be life-saving. For instance, in meningococcal infection it can be very difficult to differentiate the early symptoms of meningococcal infection from other infections and we think that it is very important for parents to be alert. We do not want patients to think that antimicrobials are dangerous for the individual and so to deter people from seeking them or taking them when they are prescribed. They are, in fact, among the safest medicines, so it is very important that we maintain a balance and avoid giving what may be confusing messages. As far as changing doctors' practice is concerned, there are many reasons in addition to patient expectation why a GP might prescribe an antimicrobial where one might not be indicated. Most antibiotics are given blind, that is without knowing the actual cause of the infection. Arranging investigations may often cause delay which may be undesirable.

760. Or it could be desirable, could it not?

(*Tessa Jowell*) Yes, it could be, you are absolutely right. This is the difficult balancing judgement that doctors have to make. More explicit guidelines may help with feedback to individual GPs so that they can compare their usage with the norm. I think that sort of benchmarking, linked with public and professional education, will steer us to the right balance in what is a tricky area.

761. As one goes into a doctor's surgery these days there are noticeboards around and quite eye-catching leaflets and everybody has to wait in doctors' surgeries so there is a captive audience, which I think is good news. I am also particularly aware of the fact that it is nearly always mothers who are taking children to the doctor, and they are very anxious as to whether it is meningitis or is it something as ordinary as flu? They do not know, and obviously the doctor has the balance of judgement. You were mentioning public information campaigns which are expensive. Press releases are not. Women's magazines are looking for things to publish and if you get something eye-catching in a press release I think women's magazines are a very useful means of bringing to the average female member of the public the complications. You would have to do it in simple language, but I think they could be capable of taking in a good deal more information.

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(Tessa Jowell) We are very keen to use any medium we can in order to get good health messages and good health information across to people. I absolutely agree with you that in many cases a piece in women's magazines may reach far more women than a leaflet sitting in a public library or even in the doctor's surgery. You are absolutely right, and that is very much in tune with the sort of approach that we want to adopt. I hope what my answer indicated was the complexity involved here in getting the balance right, because what we do not want to do, having raised public awareness and, through the Meningitis Society, raised awareness about symptoms of meningitis, is to deter parents from acting on the information in what will always be a small number of cases, in order to save their children's lives. Getting the balance right is terribly important. I do not know whether the Chief Medical Officer would like to add anything.

(Sir Kenneth Calman) I think that is precisely the issue. It is getting the balance right, and also it has to be disease specific, if I can use that phrase. If a child has the symptoms of meningitis, antibiotics are extremely valuable. For a middle aged gentleman with a bit of a cold, then investigations might help to clarify that, and might help to put you on to the right antibiotics. It is disease specific, and the balance between giving information, saying you do not need an antibiotic, and at the same time wishing people to come early for the antibiotic I think is quite difficult. I am hoping that the SMAC report will give us quite a lot of help on that, and that will then be the trigger to begin a greater public information strategy which, linked through the women's magazines and other magazines, could be very helpful indeed.

Lord Rea

762. As a general practitioner, I would be interested to know, and you have already indicated, whether any of these messages for whatever medium will be done with the advice of the people at the front line, the Royal Colleges and the BMA. Following that, it is true that one of the graphs in your evidence shows that the more deprived the area the more antibiotics seem to be prescribed. This may be due to what you were talking about earlier, that the shorter the consultation the more temptation there is to give an antibiotic. This would indicate that the raising of the standards of general practice, particularly in deprived areas, should have a very high priority. I hope you will confirm that this will be one of the issues that will be addressed when that is carried out.

(Tessa Jowell) Chairman, that is an extremely important point that Lord Rea has raised, borne of professional experience. It is important that we understand the enormous variations in the incidence of infection and prescribing in different parts of the country, even between different parts of cities, and being clear about whether this is attributed either to a differential incidence of infection or whether it reflects different prescribing practices by GPs. We have to unravel the complexities of this issue in order to ensure that we put in place the right solutions and we need to be able to distinguish one from the other. Referring

back to Lady Platt's question, and in regard to patients in deprived areas, we need to be more purposeful in getting information across and available through media other than just the leaflets in the public library. We hope that healthy living centres, which we see very much as part of our public health approach, will be places that will provide good information for people. The first wave will very much be focused in deprived areas, and they will begin to make some medium to long term contributions to these disturbing discrepancies.

Lord Perry of Walton

763. MRSA is relatively uncommon in the general population but it is becoming quite common in hospitals. If vancomycin resistance comes as well then MRSA is untreatable. If it gets into the general public the risk to numbers of people may be greater than the risk of meningitis. The balance has to be put in the right way.

(Sir Kenneth Calman) I think that is a very important point, and clearly it is one of our concerns that the introduction of vancomycin resistance is going to tip the balance. In reference to Lord Rea's point, the question is why children in deprived areas seem to have a high risk of infection anyway. That takes us into the broader government strategy in relation to the health of the nation, about inequalities and about housing which are clearly very important. The second thing which I think is relevant, and this will also come out of the SMAC report, is that if you decide that a child does not get an antibiotic, then the parents need to be very clear on what to do then. It is not simply a case of going back if you are not feeling well. We need to be much clearer, and our colleagues in general practice also have to be much clearer, about recognising and telling people not just to come back when they are unwell, but there may be specific things.

Lord Rea

764. It takes time, as we hear frequently.

(Sir Kenneth Calman) Yes.

Lord Jenkin of Roding

765. We have had a lot of evidence, particularly from clinical microbiologists and others who are specialists, which, I have to say, has alarmed the Committee. I get the impression that the threat that we face in the development of resistant organisms is probably more serious than has hitherto been recognised, certainly by the public, but I would suggest by a lot of policy makers. The first question is, are we right to treat these warnings by the clinical microbiologists at their face value? If it is right, then I think we have to act a good deal more firmly than perhaps your answers so far have indicated. The second question is that, yes, of course, there has to be a balance but the problem is that it is not the patient who develops resistance, it is the microbe. Therefore, you are balancing a potential, perhaps quite small advantage to the patient by administering a drug

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whereas you are contributing to the development of the whole process of resistance. Does the Department recognise that there is a dilemma and that perhaps your rather careful balance does not pay sufficient attention to the real threat that is now facing not just this country but overseas as well?

(*Dr Cooke*) Clearly, I think that the warnings given by the clinical microbiologists should be taken seriously because what we are looking at is the long term evolution of a problem which is inevitable, that while we are using antibiotics, organisms will become resistant. I think we have to take these views very seriously, and at the same time recognise that what we have to set in place are long term initiatives which will deal with this problem, which is not going to go away. As long as we are using antibiotics the problem is always going to be with us. We have to set in place initiatives that will deal with this problem over a very long period of time.

(*Sir Kenneth Calman*) The reason for raising it in the annual report a couple of years ago was precisely because of my concern about this. I would not wish to dissent from what you have just said. I am concerned about it. The balance to which I was referring was the balance between public and professional education and how far you go one way saying do not take antibiotics until the profession has had time to do something. As Lord Rea has mentioned, it takes time in the consultation to do that part of the process. I am very much with you in terms of the concern. Indeed, that is why I raised it.

Baroness Masham of Ilton

766. What hope is there of getting a quick test so that the right antibiotic gets to the right infection, in other words, speeding up the tests?

(*Sir Kenneth Calman*) That is part of the very big research agenda but it does take time. As you no doubt have heard from other specialists, a simple test in the GP's surgery for resistance or indeed for activity is not available just now. It might well be available but would require quite different technologies from the technologies that are currently being used. I think that is the problem.

Lord Walton of Detchant

767. The importance of this issue is heightened by the information we have received from a considerable number of witnesses in industry and elsewhere that most of the newer antibiotics have been created by modifications of existing classes of antibiotics, and the chances of any similar development of this kind occurring in the foreseeable future are rather remote. A lot of exciting work is going on in the field of molecular biology with the ultimate objective of producing many new classes of antimicrobial agents. All the evidence strongly suggests that this is a long term process which will take a good many years. I think this is one of the reasons why initiatives about which you talk are so important at the present time.

(*Sir Kenneth Calman*) That is why the research base is so important, and that research base is not just

in microbiology, but may be in other areas too, such as molecular biology. We need to look for new triggers, new targets, new ways of thinking about this. We have the best drug industry in the world in this country, very creative and very innovative, and we have had a lot of discussions with them as indeed the Medical Research Council has in trying to take this further.

(*Tessa Jowell*) I would like to wrap that up in response to Lord Jenkin's question by saying that from a policy point of view, the Government's approach is absolutely clear, that when we are presented with evidence from experts in any field and clearly experts in the microbiological field, that will be subjected to rigorous scrutiny, and where there are clear policy recommendations and implications for clinical practice, we will ensure that they are acted on. As I said right at the very beginning, our concern is, first of all, to keep this in its proper context and proper proportion, to look at what may be trends in the future and to keep ahead of the problem rather than having to face its consequences without proper strategic planning and preparation. I hope that in setting out the detailed elements of the many faceted strategy that we have, we have assured you of our absolute determination to do that.

Lord Winston

768. Minister, I must say I am rather alarmed by your answer because I think it has come to the attention of this Committee increasingly that one of the problems has been the lack of really solid information, given that there is not sufficient technology at all sorts of levels to make judgements. One of the key issues is the standard of the Public Health Laboratory Service and the fact that there is a climate where it is not really able to do that research which is perhaps needed, and its funding is not adequate and it certainly has not been compensated for inflation. Do you not think that there is a real case for trying to improve the information that we are getting by looking at the Public Health Laboratory Service?

(*Tessa Jowell*) Of course, there is always a case for making sure that we have the best possible information available. That is why we have expert committees to advise us on that. The Public Health Laboratory Service is an indispensable resource in protecting the public. It is highly regarded and in relation to the issues about its funding, I know that this has been a matter on which there has been communication with your Committee in the course of your enquiry. The accountability review is currently taking place. I will be meeting with the PHLS towards the middle of this month, and will listen very carefully to the case that they make. But I should make it absolutely clear that the PHLS is not being treated differently from any other part of the centrally funded public health functions of the Department of Health.

Chairman

769. Perhaps we could move on, as I am conscious that you have a limited time to be with us, to the use of antibiotics on animals and the veterinary field. You

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mentioned that in your opening comments. We have been aware of widespread concern in the medical community that problems of resistance may be fuelled from food-borne pathogens such as Salmonella. We are aware that you have the Advisory Committee on Microbiological Safety of Food looking at this with a promise to report some time shortly. I am wondering if you or your colleagues might wish to comment on the animal growth promoters and the progressive removal of those, as recommended by a WHO meeting in Berlin recently. Would you also comment on control of fluoroquinolones for animal use as has been done in the USA, apparently on advice from the PHLS, and what would be the role, if any, of the Food Standards Agency in this?

(Tessa Jowell) I would like to ask the Chief Medical Officer to deal with that.

(Sir Kenneth Calman) The WHO meeting in Berlin was a very important one because I think it signalled the international concern in this area. It is partly about growth promoters, but the issue around things like agriculture shows just how dangerous the situation can be. It is very real. What we do have to wait for is the Advisory Committee on Microbiological Safety of Food. We have asked them for their advice and hope that we will get that. The relationship between that and the Food Standards Agency I think will depend upon the advice. The Food Standards Agency may be able to take forward and implement any of the actions that come out of the Advisory Committee's report. The area is one of significant concern. It has been flagged up internationally, and I support the concerns that there are about this.

Lord Jenkin of Roding

770. On the question of the ACMSF working group, is that specifically being asked to address this contentious issue of how far the use of antimicrobials in animal husbandry is actually contributing to the build up of resistance and affecting human health? That is something which some of our witnesses have denied, although I have to say that I have found their denials a great deal less convincing than some of the other evidence we have had that says that of course there is a connection.

(Sir Kenneth Calman) As I understand it, antimicrobials used in the treatment of infections and as growth promoters in animal husbandry will be looked at by the Advisory Committee on Microbiological Safety of Food, yes. I think that is an area they will look at. It is part of the food chain and it would be difficult to look at the food chain without thinking of the growth promotional side as part of that.

Lord Perry of Walton

771. Someone could find the Food Standards Agency a safer home than MAFF.

(Sir Kenneth Calman) I think the outcome of the report may well be taken forward by the Food Standards Agency.

Baroness McFarlane of Llandaff

772. Sir Kenneth has already mentioned the need for effective infection control strategies, and yet we have been told that the previous government's policy of maximum bed occupancy militated against basic elements of hospital infection control, such as the availability of isolation wards, standards in cleaning, bed-spacing and ability for ward closure. I was interested in paragraph 106 of your report where the Scottish working group's recommendations say: "all general hospitals need to have sufficient isolation facilities available, either in suitable side rooms on general wards or in a separate isolation ward, or both". So there seems to us to be a conflict in priorities between maximum bed occupancy and effective infection control. Do you see a way through this conflict of priorities?

(Tessa Jowell) I would like to bring Mrs Stephens in to deal with this from a nursing point of view. What is clear is that part of the achievement of modern clinical practice has resulted in shorter hospital stays and, therefore, the increased use of hospital beds benefiting patients in terms of reducing the risk of prolonged immobilisation and reducing the length of time during which infection could be acquired in hospital. The increased movement of patients between hospital wards also necessitates added vigilance with the recognition that good practice in admitting patients to emergency admission units and thereby improving their clinical care may affect their risk of spreading an acquired infection. All hospitals are expected to have policies for infection control and to enforce the guidelines that were attached to Circular HSG 95/10. In the Cooke Report, prepared by Dr Mary Cooke, from which that guidance was derived, maximising bed occupancy does not prevent good practice being implemented although faster throughput increases risk, for example through increasing frequency of changing bedclothes, and necessitates a greater emphasis on surveillance of acquired infection and risk assessment. The PHLS has recently published the results of a study funded by the Department of Health on surveillance policies and practice in the control of infection in hospital which included recommendations for good clinical practice. Such good practice should in our view be compared by the hospital Control of Infection Committee against current standards and implemented and acted on as necessary. The role of the hospital Control of Infection committee is crucial in terms of supporting the infection control team in their work. Bed spacing, again a factor in controlling infection, is dependent on the availability of gases and other services rather than necessarily the pressure to admit further patients. Closure of a ward is a serious decision but closures do occur where necessary. Improved co-operation between hospitals has resulted in contingency plans to share pressures where necessary. Again, good practice includes tertiary referral hospitals admitting patients when they are transferred from other hospitals to single rooms until the results of MRSA testing are available. Ultimately patients who acquire infection result in increased hospital costs due to extended length of stay. So the application of infection

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control standards is therefore of direct benefit, of course to the patient but also in terms of delivering cost-effective care. Risk assessment, which has been part of good practice, will become incorporated within the whole clinical governance mechanism and it is a discipline which is being constantly refined. The clinical governance mechanisms were set out in the Government's recently published White Paper on the National Health Service. We believe that the explicit framework established for clinical guidance will ensure greater control of practice than has been the case until now. I would like, my Lord Chairman, with your permission to ask Mrs Stephens to add to my remarks in terms of the consequences for good practice in nursing.

(Mrs Stephens) Certainly the improvement of infection control policy is a key issue in relation to all hospitals, so continuous improvement is obviously important. The decisions taken, and obviously infection control nurses as members of the infection control teams are very much part of those clinical decisions that are made about patients, are really quite complex in the sense that they do need to take on board the needs of the patients themselves, the needs of vulnerable patients in the surrounding areas and obviously to some extent the needs of management and the availability of bed spaces. All policies will take account of the availability of single rooms. Cohort nursing where patients are brought together in a specific area and nursed with special nurses is another way of dealing with this problem. Of course, some hospitals do have separate isolation facilities and isolation wards. The evidence in relation to specific isolation wards, however, in relation to the case both in America and here, is not terribly clear and I think the Cooke Report mentioned this. What an isolation ward it does do is bring together infection control nurses, who are likely to maintain very good infection control practices, but of course that has to be balanced with the other clinical priorities of the patients and the need for specialist nurses in those areas. Each decision tends to be very much an individual one taking on board all of those factors.

Baroness McFarlane of Llandaff] If I may, Lord Chairman, there does seem to be a gap between the ideal advice and practice and the evidence given to us by infection control nurses that they are experiencing difficulty, and increasing difficulty, because the side wards they used to have for the isolation patients are no longer available and they are experiencing this reduction in the specification for cleaning that Trusts are accepting and many other factors, even down to the buying of cheaper soaps that cause abrasions to the hands and then infection. There are many factors of economy that it seems the infection control nurses are finding are militating against effective infection control.

Lord Walton of Detchant

773. May I ask if there are measures in place requiring training not just for doctors and for nurses who work closely with patients but also for ancillary staff, particularly following the contracting out of

domestic services? There is a lot of evidence that we have heard suggesting that the standards of hygiene generally in hospitals are not as good as they might be and that even the cleaners and many others require training in hygiene standards and infection control.

(Mrs Stephens) Certainly in the training of both nurses and doctors, there are clear programmes in relation to both pre-registration training and follow-up training in hospitals, often organised by infection control nurses. In relation to care staff and domestics, etc., again they should have infection control as part of their training programmes. If they are undertaking, for example, NVQ qualifications that will be quite a big element of their training. Certainly the policies are there and infection control teams are there to make sure that this training is undertaken. I am sure that there are areas where improvements can be made. I think certain recent research has demonstrated that.

Lord Jenkin of Roding

774. We all found the evidence of the infection control nurses very telling. I think they summed up very well the difficulties of getting sufficient priority for work to prevent something happening, which if you succeed has nothing to show for it, as opposed to work which is actually going to have a tangible, immediate impact. That is a very real psychological problem for managers and boards and so on.

(Tessa Jowell) I think that is a terribly important point, Lord Chairman. I would just like to underline the importance that the Government attaches to getting consistency of practice throughout hospitals. As Baroness McFarlane made very clear, this is an area where the level of control in a human service, if you like, is as good as the weakest link. We do need first of all very clear guidelines and, secondly, rigorous surveillance that those guidelines are actually being applied in practice. I think Dr Mary Cooke would like to add to the remarks that have already been made.

(Dr Cooke) I really wanted to talk about this question of conflict between high bed occupancy and infection control. I think one way towards a resolution of that conflict, or at least ameliorating it, would be that as the recognition of the adverse effects on the availability of beds of serious hospital infections gradually becomes realised, then it will become clear to people that the need to prevent this happening is very great. There has been a considerable amount of work now showing the effects of infections in hospitals as regards lengthening periods of stay. I think one of the things that would be enormously helpful would be for this information to be widely disseminated when it becomes available fairly shortly. This will bring to the attention of managers and to everybody in the hospital that infections themselves do make bed occupancy more difficult and I think would provide an impetus and a way to resolve this problem.

Baroness Masham of Ilton

775. We did hear a tremendous amount about the basics of washing hands but it is not just that, it is the stethoscopes and doctors' ties dragging from patient to

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patient, and even bios. It is also the agency nurses that go from hospital to hospital and are still wearing perhaps only one uniform. I know one Australian nurse from a private agency told me that she was only given one uniform. There are a lot of issues.

(Tessa Jowell) Yes.

(Sir Kenneth Calman) First of all, this is an issue for senior management in the Trust, in the community, and it is an issue which they need to take very seriously. It has to pervade right through the organisation. Secondly, it is about managing risk. Any organisation can reduce its risks by thinking ahead about how it can do it and that, as Baroness McFarlane has said, is all about how you manage the service. Thirdly, it is about reducing costs because by better management of the potential risk you can reduce the costs. People who are infected stay in hospital longer, they block beds, they bring closures, as opposed to managing it from the top. The point is very well made.

Lord Dixon-Smith

776. Minister, given that bacterial resistance to antibiotics is an inevitable consequence of the use of antibiotics, the best we can hope to do is to devise strategies which will prolong and delay the time before resistance is established. It seems to me one of the keys to developing those strategies is going to be the question of information. It has been very impressive to us how much information there is available from some sectors, such as the Health Service, and how little there is available in others. It is also clear that in one or two places some really pathfinding work has been done on pulling this information together at specific areas and making real use of it to the benefit of doctors and indeed the hospitals. We gather you are consulting on amending the Public Health (Control of Disease) Act to make laboratory reporting mandatory with certain resistances. This is certainly something that many of our witnesses have supported in their evidence. Will the list of reportable findings include MRSA? Will feedback from the Public Health Laboratory Service to the providers of the information be enhanced because without this the exercise is not going to be a lot of good?

(Tessa Jowell) Thank you very much. As you recognise, imposing a statutory duty on laboratories to report certain specified test results, including any antibiotic resistant bacteria, will require primary legislation. We will shortly be setting up a consultation on this and other proposals to update the present legislation which we believe to be in need of review and further strengthening. Decisions about which microorganisms should be notifiable would be made once the Bill has completed its passage through Parliament based on advice from an expert working group and could be modified at a later date according to need and in the light of the emergence of new strains for instance. So while I obviously do not want to pre-empt the working group's decision the final list might well include, for instance, multi-drug resistant TB and MRSA. One of the central aims of establishing a system of statutory reporting by laboratories is to enhance the quality of surveillance data that would be

available to inform practice both at a national and at a local level. Feedback on data to the providers of information is also an essential component. Information generation is very much a two-way street. The provision of information is part of surveillance but also feedback after analysis of the implications of the information provided is, as I say, also very important. The PHLS are committed to this in principle. We are confident that the enhanced data from any new system should be provided regularly to all those who have an interest both in collecting it and then using it.

Lord Dixon-Smith] I wonder if perhaps Sir Kenneth would care to comment on the managerial problems of trying to develop and co-ordinate the information services across the health service as a whole. This seemed to be an area from the evidence we have heard that is not particularly well handled at the present time.

Baroness Platt of Writtle

777. And it needs information technology desperately, it seems to me.

(Sir Kenneth Calman) First of all I agree. Without basic information as to what is happening it is very difficult to predict and plan, so that is essential. Secondly, we need to have within the National Health Service, although some of this goes beyond the National Health Service too which is quite important, an information system which captures that. That can be done through PHLS and other organisations but also within the National Health Service itself and the information technology strategy will be very much a part of that. There are issues about confidentiality and some of the discussions we have had, for example with the British Medical Association, mean that the sharing of information and the confidentiality of patient data also has to be very much part of that if we are discussing serious infections or difficult infections. I think the last point is that in the discussions relating to the Bill, or a Bill, then what I would not want to happen is that it would be drawn so tightly that we only looked at tuberculosis and staphylococcus. We are going to need the regulations to add vancomycin when it is permitted. I hope that flexibility will remain because the world is going to change over the next ten or 20 years and we need the flexibility to measure the things that we need to measure. Perhaps that is the final part, we need to be measuring the right things and capturing the right data, not just data across the board which does not have the planning of the service.

Lord Walton of Detchant

778. The opening statement you gave, Minister, made it clear that you are working towards the principle of developing a national strategy for systematic surveillance of resistance; this has been proposed by many of our witnesses. We understand that the PHLS and the British Society of Antimicrobial Chemotherapy are already having discussions on developing such a system which would be very dependent, as Baroness Platt has said, on information technology. Do you have plans to increase

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collaboration in this field with Scotland and Northern Ireland where the PHLS, of course, does not have authority?

(*Tessa Jowell*) As you say, a large bank of information on the extent and the trends of microbial resistance is available from current surveillance systems and from special studies. We do recognise, as I think we made clear in our evidence, that some of the data collected has often been unrepresentative and has been largely organism-based up until now and more robust data is available for some organisms than for others. In our evidence to you, paragraph 9, we make clear the difficulties of comparability. So it is important that we see further development of the surveillance of antimicrobial resistance, to monitor trends and in order to inform clinical practice. We support a strategic approach to this. We would expect that to be considered, as I think I have made clear, within the context of an overall PHLS surveillance strategy. We are also aware of the BSAC working party to which you have referred. We are also aware that both PHLS and BSAC are in discussion about collaboration over the development of such a strategy. We need to be in a position to be able to consider the detailed proposals before making any commitments obviously about the extra resources that this may entail. Certainly in relation to your point about collaboration with Scotland and Wales, I certainly hope that we can act. We made it perfectly clear if we take the Food Standards Agency, for instance, that we want people no matter where they live in the United Kingdom to be guaranteed similar confidence in the safety of food. I think precisely the same issues apply here.

Lord Winston

779. Minister, there is a bit of a catch 22 situation here because, of course, without the best surveillance we do not absolutely know the size of the problem and that is really the issue with regard to the contribution to the PHLS which has been falling over several years and is projected to fall further. We take your point that the PHLS is not being treated differently from other funded services, as you mentioned, but I think the evidence we have had is that it is a very key service with a regard to microbial resistance. I think what we would hope for is perhaps some undertaking, that if it could be shown that this is really a very important area, you would at least consider the funding of that service.

(*Tessa Jowell*) I touched on the answer to part of Lord Winston's question earlier on, making the point that the PHLS has been treated in exactly the same way, as you recognise, as other similar public health bodies. Of course we understand its importance. Of course we understand the critical position it holds in ensuring public health and rapid control, understanding the nature of infection and communicable disease and then placing us in the best possible position to be able to control that. Specifically in relation to PHLS funding, I would say three things. The first is that I am not going to give any undertakings at all at this hearing, and I am sure you will respect that, about the

levels of funding for the PHLS. That is a matter that we will look at in detail with them in the course of the accountability review. Of course, this is precisely the kind of issue that the Comprehensive Spending Review has been established to examine, and examine this issue it will. I hope that although it may not entirely satisfy you it leaves you in no doubt of the seriousness with which we take the need to ensure that the National Health Service is competent and adequately resourced in order to meet this challenge.

Lord Perry of Walton

780. Many people, including the MRC and I think the National Health Service research people, have not really been very sympathetic to regarding surveillance as research. At the present moment in time with the problem that we face, it very much is research and desperately-needed research. It seems to me that is another way in which help could be given, not only to PHLS but also to other people who are interested in surveillance. I do hope that ways of solving this problem can be found.

(*Tessa Jowell*) There are two points here. One is that I am concerned that the way in which research budgets are presently constructed does not necessarily mean that public health issues are given a proper opportunity to have a bid for resources. I am concerned about that and intend to look at it. The second is that I am also concerned to ensure that the research that is commissioned is the research that is needed to fill gaps in our knowledge and that the research we commission is research whose conclusions can be applied in practice. We do feel that the best way in which we can proceed is to make sure that we have good evidence on which to base our policy decisions. I am well aware of the problem to which you allude, it is a problem which extends beyond simply research in the area of surveillance. I think that it is a fundamental problem about the structure and nature of public health research and it is one we intend to tackle.

781. It would be very useful if the Department could make the right noises in its relationship with the MRC to try to persuade them to do something as well.

(*Tessa Jowell*) Right. I had a meeting with the MRC last week and they are under absolutely no illusion about our concern.

Lord Walton of Detchant

782. Would it not also be a very proper use of central funds for health service research under the Culyer initiative?

(*Sir Kenneth Calman*) I think Lord Perry and Lord Walton are indeed correct. The NHS funds are about research and development. Much of this is developmental-type research as opposed to very basic research. Even simple issues like agreeing definitions between Scotland and England about what an infection is and how we record it, all of these are quite important developmental issues which I think is the proper way of looking at the research funding as well as the molecular biology. If I can again support what the

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Minister said about our links with the MRC, these are very strong. They had a meeting, as you probably know, last week about antimicrobial resistance. I suspect, like you do, that some of the answers are going to come from slightly unusual places and not necessarily by having a directed programme all the time because of the problems of knowing quite where they are going to come from. The surveillance issue is critical to this and unless we do have proper surveillance then we will not be able to answer very many of the questions. Indeed other issues that you may raise with us, for example about drugs and the ability to know which drugs have been used in hospital or in the community, fall in exactly the same kind of category, the need for planning information is precisely the same.

Chairman

783. Minister, we are conscious you need to get away so we will break the questions at this time.

(*Tessa Jowell*) Thank you very much indeed, Lord Chairman. It has been a pleasure to answer your questions. Let me just underline the importance that the Government attaches to your enquiry.

[*The Minister withdrew.*]

Lord Walton of Detchant

784. We have had some very helpful information from the Prescription Pricing Authority about the range and extent of costs of prescribing of antibiotics in general practice. But so far as the hospital situation is concerned, as you said in your submission, there is no central point for amalgamating data from hospitals in the United Kingdom and many hospitals, indeed the majority of them, cannot even present their own prescribing information in a form suitable for analysis alongside resistance data. It seems to us that it would be very helpful if a mechanism could be introduced whereby we could get similar information to that available in general practice relating to hospital prescribing. Have you any plans to pursue this?

(*Sir Kenneth Calman*) This is clearly a very important part of information gathering too for the planning of the service and I would like to ask my colleague, Dr Winyard, to respond.

(*Dr Winyard*) We accept this is a real issue. The obvious discrepancy between hospital and general practice in this respect is due to the way that information systems have been developed to support prescribing in the two environments. I think all hospitals will have a pharmacy computer system, but as perhaps 80 per cent of the drugs prescribed are issued down to wards in bulk form as opposed to being designated for individual patients, one cannot do the detailed tracing that is possible in primary care because of the individual prescriptions issued by GPs that drive that system. A small but increasing number of hospitals are installing computer based prescribing and that also has tremendous advantages because it can enable the doctor, often a junior doctor, doing the prescribing to have instant access to prescribing policies, drug interactions, that sort of thing. That is

still on a small scale. What we are doing is we are funding the National Prescribing Centre to run a pilot in ten hospitals to see how these different streams of information can be brought together to yield comparable information. I think the thing to bear in mind is that because it is not possible to aggregate this data centrally it does not mean that it is not scrutinised locally. Each hospital will have a drugs and therapeutics committee that is writing the hospital formulary which will include antibiotic prescribing. So at a local level they are able to look at their pattern of use of antimicrobials and relate that to local resistance patterns and if necessary change the formulary if that is indicated.

(*Sir Kenneth Calman*) I think it emphasises the importance of the role of the pharmacist in the hospital and indeed their expertise in helping us in this area.

Lord Jenkin of Roding

785. A lot of the evidence we have had on this was the absence of any denominator against which you can assess the prevalence of resistance. If you do not have an effective system of making sure that you have that denominator information it is extremely difficult, indeed it is almost an impossibility, to detect trends; all you are getting is the things that the laboratory says should be forwarded, you are getting all the details of the resistance and not the generality against which you base that.

(*Dr Cooke*) The question here is developing laboratory systems which will pick up denominator data, which will pick up sensitive organisms as well as the resistant ones. There are still a whole lot of other problems about this surveillance when one has done that. I think a number of laboratories can already do it. If this could be made more general then we could collect denominator and numerator data and that would be enormously helpful.

Chairman

786. Perhaps we might go on now to nosocomial infection surveillance. We were pleased to see in your report that NINSS has been set up. We consider that an important step forward in the surveillance of hospital infections. We wonder if it has been modelled on the United States National Nosocomial Infection Surveillance System. Those of us who visited the USA were very impressed by CDC's ICARE project, that is Intensive Care Antimicrobial Resistance Epidemiology. I particularly was most impressed by what they were doing. Would you support a similar project here, possibly in collaboration with the CDC and the ICARE programme and clearly, of course, the resourcing of such a scheme comes with it?

(*Sir Kenneth Calman*) The resourcing is an issue which we will take up with Ministers. If I can ask Dr Winyard just to say a little bit about the scheme itself and how it will develop.

(*Dr Winyard*) I think you have heard something about the Nosocomial Infection National Surveillance Scheme. It started last year with joint funding from us and the PHLS. The plan is to develop a series of

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modules looking at specific sorts of infection. There are two up and running so far, one looking at bloodstream infections which started last spring and the other at certain sorts of wound infections which started in the autumn. Already 150 hospitals have participated: so that is very encouraging. We have learned a lot from the US experience, including some things not to do, and are watching the development with interest. Certainly it will be an interesting idea to think about an ICU module that might well look like ICARE. I know Dr Cooke has been involved in a lot of the detail of this.

(*Dr Cooke*) As part of the scheme data on the antibiotic resistance of the organisms causing the infections is being collected. That in itself is useful data. Clearly it would be more useful if it could be related to antibiotic prescribing in those areas. It should be stressed this scheme is at an early stage. Just getting a national scheme like this off the ground is quite a time consuming and difficult business. There is the beginning of this sort of collection of data. This is a distinct possibility.

787. Yes it is essential, we think, to have prescribing information in such a scheme which there is in the ICARE programme. It has been embraced in the States very well and there is feedback to the individual institutions on a confidential basis. It did seem to us that it was a very successful scheme and the participants were very enthusiastic.

(*Dr Winyard*) That sort of feedback is a feature of our scheme, both enabling hospitals to see their own position in relation to others and also making available advice about how to look into things if they appear to have a problem.

(*Dr Cooke*) Can I just add to that. As soon as enough data is available hospitals will see their own antibiotic resistance patterns against a national background. I think that will encourage hospitals who see that they have more antibiotic resistance than is general to begin to look at their prescribing.

Lord Rea

788. One of the advantages of the ICARE scheme was that the prescribing patterns of antibiotic usage in those institutions was collected. It seems to me if this is just getting off the ground it might be useful to concentrate on those hospitals or laboratories with catchment areas which are contributing to the NINSS scheme.

(*Sir Kenneth Calman*) I think this also reflects the need for a cohesive strategy that brings all of that information gathering together and makes the maximum use of it, first of all so that it is better for patients and the public but also so that we can learn as the programmes develop themselves.

Lord Perry of Walton

789. You appear to blame overuse of expensive new antimicrobials partly on over-promotion by the pharmaceutical industry. The pharmaceutical industry denies this very strenuously. Do you really believe that

it is a major factor? Is there a need for anything else to be done?

(*Sir Kenneth Calman*) Far be it for me to take you to task but I think the words used actually were "heavily promoted" rather than "over-promoted" and that is a difference. Our relationships with the pharmaceutical industry in this area are clearly very important in the development of new drugs. The two which are particularly mentioned in paragraphs 65 and 69 are the fluoroquinolones which are an important class, but secondly the macrolides. That coincided, I think, with the management of helicobacter which was in a sense at the beginnings of a new indication. It is not in that sense surprising that there were more antibiotics used. We go very clearly by the ABPI Code of Practice. Relationships with the pharmaceutical industry are good. There is concern, as there always will be, about over-promotion as opposed to heavy promotion and that is an issue which myself and my colleagues in medicine generally take seriously. I think both through the ABPI, the General Medical Council and professional organisations we want to make quite sure that we get information from the pharmaceutical industry, which is terribly important, but at the same time use that appropriately.

790. I think heavy promotion is to be expected when a lot of money is spent on the drug. In this particular case they stand to lose if it is over-promoted and used unnecessarily and thereby creating resistance, it is against them. One would not expect them to be particularly guilty in this field.

(*Sir Kenneth Calman*) I think part of it is that there are some new indications, particularly in the macrolides, which may well have been related to that. I think that is right, that over-promotion and over-use will reduce the effectiveness of the drug in the long term unless it is managed properly. Again, I hope that the SMAC Report may well help us with that as well.

Lord Jenkin of Roding

791. I was impressed by the lack of knowledge of many of the clinical microbiologists as to what the drug industry was doing. They were wringing their hands and saying "There does not appear to be anything new on the horizon at all", but then we got the ABPI and two or three companies along and we were impressed with the amount of money that they are pouring into research, particularly into genome research and trying to unravel some of the mysteries of this and eventually find out where resistance is coming from. Is this something that the Department is able to keep in touch with, bearing in mind, of course, the inevitable commercial confidentiality in this industry?

(*Sir Kenneth Calman*) Yes, very much so. Because we have a very strong pharmaceutical industry in this country the last thing one wants to do is to damage that at all. I have had personal contact with a number of pharmaceutical companies at the top level to discuss this very issue. They are actually putting a great deal of money into this just now. If we take tuberculosis, the identification of the TB genome may well give us a completely different way of thinking about

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antibacterial therapy. I am certainly aware of what is going on in the area. The fact that there are not lots of new drugs coming out does not mean to say there is not a lot of work going on in this area and a great deal of investment. You will have heard that probably from the industry itself.

Lord Perry of Walton

792. The only difficulty is when they have done their research and they have spent enormous amounts of money on it, they will then have 15 years before it comes on the market.

(*Sir Kenneth Calman*) I think this is the case with most drugs. What we want to do, and the European drug agencies and others, is to try and speed up the process. That has to be with public safety in mind all the time. That is always a balance between developing new drugs and the safety of drugs.

793. I did not mean that, what I meant was resistance will have increased a good deal in 15 years.

(*Sir Kenneth Calman*) Yes, I understand that.

Lord Porter of Luddenham

794. The Minister spoke quite encouragingly about this country's better control of over the counter antibiotics than perhaps some of the other countries in Europe and elsewhere. There is a very strong pressure building up it seems for more over the counter antibiotics. This is certainly contrary to all the witnesses that we have spoken to about it, including yourselves. They all say it would be imprudent to increase the ease of over the counter purchase. What controls would you like to see, and would you insist on, for the new over the counter antibiotics? Is this a matter that you can control in any way or will the result be forced upon us by the European Union who are already doing this with antibiotic dressings?

(*Sir Kenneth Calman*) First, there is a misunderstanding I think. No systemic antibiotics are available in this country over the counter. There are a number of topical preparations and local preparations, anti-fungal ones, but there are currently no systemic ones available. That is quite important. Clearly as we have emphasised throughout, and as you have emphasised, the importance of antibiotic resistance would be enhanced if these drugs were freely available over the counter. It requires public consultation and a ministerial decision for that to occur, if it was to occur. Any application from a pharmaceutical company to go from prescription only to over the counter would require again the Medicines Control Agency, the Medicines Commission and Ministers to make that decision. I think from what you have heard from the Minister already it is very unlikely that we would wish to move that way at all. The last part of your question was about the European Community and again the criteria there laid down is where there is a danger to health if used without supervision, and since that would come into that category I hope that we will be able to ensure that in this country over the counter

preparations will not be available. That is where we stand at the moment.

Lord Walton of Detchant

795. There has been some relaxation on antivirals. (*Sir Kenneth Calman*) Topical preparations. I think it is quite important that these are topical because exactly the same issue would be relevant to antivirals and the influenza debate over the last year or so will recognise the importance of that.

796. The important point being that there is some evidence I am told that the use of anti-viral preparations, for instance for herpes simplex, is resulting in some increased resistance.

(*Sir Kenneth Calman*) The issue about bandages carrying antibiotics is one which the Medicines Advice Agency is clearly very well aware of and there is concern.

Chairman

797. Can I just ask you, when the European Union say "danger to health", does this mean to public health or to the patient's health?

(*Sir Kenneth Calman*) The phrase is "danger to health" and that must be interpreted either by the individual—if drugs are given by an individual to themselves would they make their health worse by drug reactions or side effects—but I hope it relates also to the broad public health consideration of that. That is such an important matter, Lord Chairman, that I would like to be able to respond formally to that question to make sure that it is absolutely clear. I have given you my verbal reassurance but it is such an important one, if you would allow me we would submit that in writing.

Chairman] We would certainly welcome that.

Baroness Masham of Ilton

798. Do you think we should be putting pressure on EU countries like Spain and Greece that they should do better, because the Minister kept on saying we were doing better than other countries? One cannot stop a resistant strain travelling from, say, Spain to Iceland and we may pick it up.

(*Sir Kenneth Calman*) I think she responded to that by saying this is an issue which has been and will be discussed, I am sure, at the Health Council. I will certainly be picking it up with my European Chief Medical Officer colleagues. It is properly a matter for the Commission to look into.

Lord Jenkin of Roding

799. I was a little taken aback by the written evidence that was put in on this by the RCGP which seemed to suggest that they would not object if some products were put over the counter. We cross-examined them on this and they backtracked fairly firmly. I was left with the impression that there is a sort of almost political correctness point that more

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[Lord Jenkin of Roding *Contd*]

of these things ought to be able to be bought directly by the customer.

(*Sir Kenneth Calman*) I think this is an issue about choice and availability and not allowing people to make up their own minds about things. There is a clear public health dimension to this. As you have pointed, out it is not just about the individual but about the population in which that individual lives and works.

Lord Winston

800. On the issue of purchasers having a responsibility to meet standards of infection control, your memorandum says "The delivery of these objectives is being monitored and reviewed through the performance management process". Would you like to tell us about the standards and indicators that you are employing?

(*Dr Winyard*) Yes. Two things, I think. There is no doubt that the prevention and control of communicable disease is a key part of the responsibility of health authorities to look after the health of their population and they accept that. We have reinforced in the most recent round of what we call "Priorities and Planning Guidance for the NHS" which sets out priorities for action by local authorities and Trusts, that protection of the public health is a priority. To look at the adequacy of control arrangements for communicable disease we asked the regional epidemiologists—they are specialists in this area funded by us through the PHLS but outposted in each of the regions of the NHS—to conduct a survey of the arrangements that are in place across the country. They fed back the results to us and now each regional office is picking up with individual health authorities where that survey showed the local arrangements to be deficient and they are developing an action plan with them to remedy whatever the shortcomings are.

801. Did you find that local arrangements were sometimes deficient? What is the record like?

(*Dr Winyard*) We would be very happy to let you have a copy of the report, it has been published. As you would imagine it was mixed. The immensely reassuring thing was that the arrangements for managing outbreaks were satisfactory across the country. What was much more patchy was some of the more proactive work that will be a very important part of an overall strategy of the sort your Lordships are looking at: proactive surveillance, developing new policies. In some places that tended to be sacrificed to the pressure of the day to day work of controlling immediate problems.

802. Were you able to identify paradigms of virtue in these?

(*Dr Winyard*) Yes. Some health authorities are doing a very good job and are active right across the range of activities that are needed both to be proactive, to pick up the problems before they occur, and tackle the immediate ones and do research and education, they have developed good policies for control in the community as well as hospitals and nursing homes. In

other places it is a much more threadbare service but we are taking action on it.

Lord Jenkin of Roding

803. The present Government has laid understandably great stress on waiting lists for elective surgery. Having experienced this until recently in a Trust, that becomes an overriding priority for a purchaser. Although we have heard evidence that of course if in the longer term you are more effective at controlling hospital infection, you will in fact actually be able to improve your performance overall; but in the short term it sometimes requires measures which are bound to lead to longer waiting lists for elective surgery. Is this an issue which the Government are now willing to take on board and recognise?

(*Dr Winyard*) Certainly the Executive has always recognised the tensions because they are very real, it is what managers, both locally and centrally, wrestle with each week, how to reconcile these very real and immediate pressures—this goes back to Baroness McFarlane's question—to keep the service going and to deal with the steadily rising numbers of emergency admissions which place tremendous strains on the system while at the same time balancing that with taking preventive action, which as you say sometimes needs to involve slowing things down, to prevent in this case problems with microbial resistance. It is a juggling act. There is no easy answer.

804. There has been huge emphasis on pinning health authorities up by the ears but waiting lists seem to be getting longer and that inevitably puts pressure on when they come to do the contracts or to get their providers to come through on that. In the short term this can militate against many of the things which you have been talking about.

(*Dr Winyard*) Yes. As part of monitoring this situation we look at things on a quarterly basis and highlight special issues with regional offices. One that was highlighted was the impact that MRSA can have in closing wards and how, as you say, it is advantageous to take steps to stop that happening.

[Lord Jenkin of Roding] Local newspapers do not always understand that!

Baroness Masham of Ilton

805. The Cooke Report recommended that health authorities should build standards of hygiene and infection control into their contracts with Trusts, paragraph 6.5. How widely has this recommendation been implemented? Do you see it as a good way to raise standards in this area, including training, and levels of specialist staff?

(*Dr Winyard*) I think the key driver in this is the wish of hospitals to provide higher quality services. That is why they will want to act on recommendations as in Dr Cooke's report. That is supplemented by health authorities putting it in the contracts but I think the impact of having a whole series of detailed recommendations on what would be a whole panoply of different subjects in the contractual process is

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inevitably limited. What it does give you is an entrée to what is happening, to insist in this particular area, for example, that the CCDC is a part of the hospital infection control team and therefore can know what is going on. Therefore, if there is a real problem locally which the purchaser should be concerned about, they will know and they can intervene with the threat of the contractual lever as a way of putting pressure on if action does not happen. The main driver is the wish of clinicians and managers to provide safe, high quality services. That is why they act on the sorts of guidance that Dr Cooke produced.

806. Do you think with the pressure of competition between Trusts that there is sometimes a cover-up? When I was on a health authority in Yorkshire we heard at a meeting with the local radio saying "intensive care unit closed for the third time since Christmas" and that was just before Easter.

(*Dr Winyard*) I could not comment on an individual case. Something that is important is in the White Paper published in December, that a greater emphasis on collaboration and not competition would remove these sorts of pressures if they were important and certainly increase the closeness of working between health authorities with their overall responsibility for health of the population and individual Trusts.

(*Dr Cooke*) The report was mainly concerned with the structural and management arrangements of infection control. I think probably one of the next steps which will be very important will be developing good clinical standards. These are in the process of being developed and will become a national standard against which Trusts can measure what they are actually doing. Of course, it does not mean that every Trust will do precisely the same thing but they will be able to look at what they are doing against these national clinical guidelines. I think that will be enormously helpful in this respect.

807. Who will monitor what the Trusts are doing? Will it be an outside body like the Department of Health? How will that be policed, as it were?

(*Dr Winyard*) There are a variety of mechanisms. Some of the ones we have heard about will rely on, for example, the PHLS feeding back information to the Trust in a comparable form about where it stands in relation to other Trusts, plus advice on what to do about it. The White Paper introduces a number of mechanisms to promote coherent quality across the NHS both by using local audits and possibly by surveys by the Commission for Health Improvement if there are thought to be differential problems across the NHS. The role of the health authorities with their overall responsibility for the health of the population will always be important here and they will want to monitor what is happening.

Lord Perry of Walton

808. With the increase of MRSA hospital infections, when open heart surgery is done under a blanket of antibiotic cover are they using vancomycin?

(*Sir Kenneth Calman*) I do not think that is one we can answer with certainty. We can provide a note

on that. I suspect there are others around this table who can give you that advice now.

809. It is a point of some importance.

(*Sir Kenneth Calman*) The other one relates to colo-rectal surgery, for example, but again I suspect there are people around here who can give you that evidence right now.

Baroness McFarlane of Llandaff

810. You refer in paragraph 118 to the fact that you are working towards new National Hospital Infection Control Clinical Guidelines. Could you tell us what these will add to the Cooke Report on hospital infection control referred to in your paragraph 105, and the new guidelines on controlling MRSA in your paragraph 115? Is it time you commissioned a Cooke-type report on infection control in the community?

(*Mrs Stephens*) First of all, the Cooke Report really set out very clearly the management arrangements for infection control and concentrated on infection control teams, the setting up of those, and surveillance, management of outbreaks, etc. What it did recognise, however, was that there did need to be more guidance on detailed procedures which would help authorities and Trusts in identifying both the policies required and detailed procedures for actually dealing with infection control. What we have done is to support the development of new MRSA guidelines and hopefully those are going to give very good advice to Trusts both in relation to the colonisation and infections of patients and the care and treatment of those patients. But infection control throughout the hospital of course is a much wider problem which involves both every patient and also a whole range of other organisms. If we take TB and Hepatitis B and C and things like chickenpox and shingles, all of these things have to be addressed in relation to a hospital environment. The new guidelines will do this. They will be very broad comprehensive guidelines which will cover all the issues and hopefully provide very good national guidance so that local guidelines can be developed. They should also link very well to the NINNS surveillance scheme through the PHLS so that Trusts will be able to examine standards alongside outcome. The guidelines will be useful for Trusts in their new responsibility in terms of clinical governance. They have responsibility for their quality systems and also need to look at adverse incidents and risks within the Trust itself. That will be hopefully soon their statutory responsibility.

Baroness Masham of Ilton

811. Some of us went to visit King's College Hospital, Denmark Hill, and they have quite a lot of staff working within the hospital on infection control but they told us that there was not one nurse employed by Camberwell in the community for infection control. That is quite a serious situation when it is the highest known area in the country for gonorrhoea.

(*Dr Winyard*) As I think I said, infection control in the community is certainly an area of weakness that

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was picked up in the survey I referred to. It would not surprise me.

812. So you will be putting guidelines out, will you?

(*Sir Kenneth Calman*) In relation to the community side of things the question was, should we do a Cooke Report in the community, and Dr Winyard will respond to that.

(*Dr Winyard*) Addressing that directly, the answer is we do not think the time is right at the moment because, as the Minister said earlier, we are seeking parliamentary time for legislation that would revise the organisational arrangements between health and local authorities in this area. There is guidance on what ought to happen but for a variety of reasons the situation is not as good as it ought to be in some parts of the country.

Baroness Masham of Ilton] It is not really local authorities, it is the community nursing medical service.

Baroness McFarlane of Llandaff

813. That is right, but also the problems of elderly people in nursing homes with MRSA.

(*Sir Kenneth Calman*) This is an issue which goes beyond infection as it happens and is about the public health side of the district and the local authority. Both within the White Paper and I hope perhaps in subsequent papers coming out the importance of the link between the health authority and the local authority broadly in terms of control of disease and improving the public health will become clearer. That is part of the legislative issue to actually tighten some of that up.

Lord Jenkin of Roding

814. A related problem to this is the shortage of people to fill posts. We have heard of clinical microbiologists retiring and the Trust in question saying they have not been able to fill the post or they are having to wait because of financial pressures. Given the amount of additional work that what we have been talking about all morning is going to involve on this, that seems to be rather worrying.

(*Sir Kenneth Calman*) Yes, it is. It has come to us too from specialists and professional associates that microbiology as a discipline, at a time of enormous excitement in microbiology and there is a huge amount of work to do, seems to have less interest in it and greater difficulties getting microbiologists. This has come to me through specialist training issues. It is not the financial issue. There are no people in the speciality or fewer people than there might be in the speciality. I think some of my colleagues are anxious to see how that might be reversed.

Baroness Masham of Ilton

815. They told us that they needed to go up the agenda, to have their profile raised.

(*Sir Kenneth Calman*) I agree with that, indeed I hope your report will do that. In my own little way I have been trying to get it up the agenda as one of the more exciting disciplines in clinical work right now.

Lord Jenkin of Roding

816. Is this something that you are addressing with the Royal Colleges?

(*Sir Kenneth Calman*) Indeed. My colleague, Sir Leslie Turnberg, in his other capacity as the Chairman of PHLS, has picked this up very quickly and is taking that all over the country through the colleges. We will pick that up. I have already discussed it but we will continue to pick that up.

Baroness McFarlane of Llandaff

817. I want to underline that you see as yet the time is not right for Cooke in the community.

(*Sir Kenneth Calman*) Not because it is not right to do it but because there are substantial organisational changes that may be occurring between health authorities and local authorities giving local authorities greater responsibility for public health matters. Once that is clarified then it becomes easier to do the kind of work that you are suggesting. I absolutely agree with that.

Lord Walton of Detchant

818. Obviously you cannot speak on behalf of the Scottish Health Department or indeed on behalf of the Northern Ireland Office. Is there an adequate level of collaboration between the PHLS and such mechanisms as exist in those two countries?

(*Sir Kenneth Calman*) Yes, I think there is. It is an entirely legitimate question to ask. There are increasing relationships between PHLS and the Scottish and Northern Ireland bodies. There has to be because this is a national United Kingdom issue rather than just an English and Welsh issue. There are lots of ways in which that, like everything else, can continue to be improved. We must see that. As I mentioned earlier, issues like definition of infection, how do we record it, using the same kinds of forms so that people get it altogether is entirely relevant. The relationships are good and need to continue to be strengthened.

Chairman

819. Any other points, my Lords? Sir Kenneth and your colleagues, we are very grateful to you for being particularly generous with your time.

(*Sir Kenneth Calman*) If I can respond, I hope you recognise that this for us is a very important issue, for patients and the public. It is something that we are taking very seriously. We hope we have developed a cohesive strategy. We look forward very much to your report. As always it is a great pleasure to come here.

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[Continued

Supplementary Memorandum by the Department of Health

1. *Question 1: Tuberculosis screening*

Baroness Marham expressed concern about the importation of drug-resistant tuberculosis from abroad. The following paragraphs give a brief outline of the current screening procedures for new entrants into the UK.

Government policy is for new immigrants from areas with a high prevalence of tuberculosis, and all refugees and asylum seekers, to be screened for tuberculosis. Immigration officers at ports of entry refer new entrants from these areas who are subject to Immigration Controls to Health Control Units where a chest x-ray may be performed or arranged if required. If this suggests signs of TB, the individual is referred to hospital for further investigation. In all cases a form is forwarded to the Consultant in Communicable Disease Control at the district of intended residence informing him of what has been done at the port, and any results, so that appropriate further action can be taken at district level.

While screening of very high risk groups such as refugees and asylum seekers continues at Ports, screening for others is done as far as possible at local level. This has the following advantages:

much of the TB in new immigrants is not apparent on entry but develops within the first five years after entry;

screening at district allows inclusion of a skin test which takes several days and is not practicable at ports; the test not only identifies those who require investigation for active TB but also those in whom specific preventative measures, such as chemoprophylaxis or BCG vaccination may help prevent TB in the future;

it allows screening to be separated from immigration controls, and also allows other health issues to be addressed.

There have been a few problems with the current system: immigration officers have discretion about who they refer, so some may slip through the net; and the notification to districts has sometimes been slow, so that the new entrants may have moved before being seen locally. A pilot study has recently been conducted to assess more efficient ways of managing this process. The results are awaited, and will inform future recommendations.

EARLY IDENTIFICATION OF DRUG RESISTANT TB

The further guidance the Department is preparing on the control of tuberculosis, which covers HIV-related and drug-resistant tuberculosis in more detail, includes lists of risk factors that should increase suspicion that a patient may have drug-resistant—or multidrug resistant—tuberculosis. These include previous treatment for tuberculosis, particularly if this was incomplete, exposure to known drug-resistant disease, and birth or residence in a country with known higher rates of drug resistance.

If multidrug resistance is suspected, it is recommended that more rapid diagnostic tests are considered and more stringent infection control measures than those recommended for drug sensitive disease are taken until multidrug resistance is excluded.

2. *Question 11: The European Directive on over-the-counter medicines*

“Danger to Health” in this context includes danger both to individual and to public health, for instance the danger of antimicrobial resistance. The requirements are very similar to those currently in use in the UK. It is up to individual Member States to apply the criteria for their own country.

3. *Question 12: The Regional Epidemiologists survey of communicable disease control arrangements at local level*

Dr Winyard promised to let the Committee have a copy of the report of the survey the NHS Executive asked Regional Epidemiologists to undertake last year within their respective regions on arrangements for communicable disease control at local level. I enclose a copy (*not printed*). If you need more do let me know.

The survey was carried out between late June and mid August 1997. The results revealed some short-comings and active steps are being taken by the Executive's Regional offices, working with districts through Regional Directors of Public Health, to improve the situation within their respective regions where this is necessary.

The report and an action plan were considered at an NHS Executive Board meeting in November and they have asked for a report in time for their June Board Meeting, setting out the progress that has been achieved since November.

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The Executive Board has taken on ownership of the action plan to ensure that this key HA function is discharged adequately in all parts of the NHS. Regional Epidemiologists have discussed the survey results with their local Consultants in Communicable Disease Control and Directors of Public Health. Agreed action is being followed up by the Regional Officer performance management systems. Regional Directors are monitoring the progress within their Regions.

4. *Question 15: Infection control in the community—the role of health authorities, Consultants in Communicable Disease Control and Community Infection Control Nurses*

Control of communicable disease and infection is an important aspect of Health Authorities' responsibilities to protect the public health. These were set out in the "Abrams Report" HSG(93)56, Annex B of which deals specifically with communicable disease control. Health Authorities fulfil this responsibility partly by direct provision of services by health authority staff, and partly through commissioning from NHS Trusts.

A new medical consultant post, now called the Consultant in Communicable Disease Control (CCDC) was created following the Acheson Report "Public Health in England". The CCDC reports to the Director of Public Health of the Health Authority and takes the leading and co-ordinating role in all aspects of infection control in the community. He or she is also normally appointed by the local authority(ies) as their "proper officer" for certain functions, particularly the exercise of the local authority's statutory powers under the Communicable Disease Control legislation.

In the community the CCDC's key responsibilities include:

- (a) surveillance of communicable disease and infection;
- (b) identification, investigation and control of outbreaks;
- (c) producing/contributing to district policies on prevention of infection, for instance on immunisation, screening of new immigrants for TB, infection control in nursing homes, etc.;
- (d) provision of advice to NHS and local authority colleagues and the public on policies and the management of individual cases;
- (e) input to commissioning.

In some health authorities, CCDCs are supported by a team including an epidemiologist and a health authority employed community infection control nurse (CICN) or public health nurse. In other districts CICNs are employed by Community Trusts or a hospital trust has contracted to provide ICN advice to local nursing homes and other institutions. Not every district currently has community ICN cover, but the numbers are steadily increasing. The salaries of these staff have now been excluded from the definition of health authority costs which are subject to management cost reductions in 1998–99; this should encourage more health authorities to employ them.

WRITTEN EVIDENCE

Memorandum by the Advisory Committee on the Microbiological Safety of Food

1. The Advisory Committee on the Microbiological Safety of Food (ACMSF), which is an independent, non-statutory body appointed to advise UK Health and Agriculture Ministers, was established in December 1990, on the Recommendations of the Richmond Committee, with the following terms of reference:

to assess the risk to humans of microorganisms which are used, or occur, in or on food, and to advise Ministers on the exercise of powers in the Food Safety Act relating to the microbiological safety of food.

2. In addition to publishing Annual Reports on its work, the Committee has reported to Ministers on a number of specific topics, viz vacuum packaging, *Salmonella* in eggs, *Campylobacter*, VTEC, and poultry meat.

ACMSF INTEREST IN MICROBIAL ANTIBIOTIC RESISTANCE

3. During the course of 1995, the Committee took stock of the position in relation to antibiotic resistance in enteric bacteria infecting animals and man, with a view to deciding whether it needed to involve itself further in assessing the situation, given the work already undertaken in this area by other bodies and agencies. Of specific interest were the use of antimicrobial drugs in humans and animals, and trends in antibiotic resistance in microorganisms associated with human intestinal infections.

4. The Committee's consideration of this issue took place against the background of concern about a rising incidence of certain antibiotic resistant enteric pathogens in humans and animals (eg multiple resistant *Salmonella typhimurium* DT104 and ciprofloxacin-resistant *Campylobacter*), the use of antibiotic resistance markers in genetically modified food organisms, and the possibility that imported foods might be more likely to contain antibiotic-resistant organisms than UK-produced foods, because of a freer availability of antibiotics to agricultural producers in other countries.

CONSULTATION WITH OTHER BODIES

5. In order to define acceptable areas of work for the ACMSF, and to avoid duplicating or cutting across the activities of other bodies with relevant interests and responsibilities in this area, the Committee embarked upon exploratory consultations with, eg the Medicines Control Agency, the Public Health Laboratory Service, the Veterinary Products Committee, and the Advisory Committee on Novel Foods and Processes. There were no objections to the ACMSF's proposals, and a number of the bodies consulted offered their cooperation. The ACMSF therefore concluded that an in-depth view of the role of food in transferring microbial antibiotic resistance should be undertaken, and that a multi-disciplinary Working Group should be set up for this purpose.

WORKING GROUP ON MICROBIAL ANTIBIOTIC RESISTANCE IN RELATION TO FOOD SAFETY

6. The Microbial Antibiotic Resistance Working Group (MARWG) was set up in 1996 with the following terms of reference:

to assess the risks to humans from antibiotic resistant microorganisms.

7. The ACMSF agreed that the MARWG's broad areas of work should be to:

- assess the likely scale of the problem of human and animal infections caused by antibiotic resistant microorganisms in the food chain;
- assess the role and importance of food and food production as a source of antibiotic resistant microorganisms in humans; and
- consider the need for any action to protect human health.

8. Membership of the MARWG is detailed in Annex A (*not printed*).

PROGRAMME OF WORK

9. The Working Group began its work in August 1996 and, by the end of July 1997 had held six further meetings. Four further meetings have been scheduled between now and the end of the year. Presentations have been received, or are awaited, on a wide range of relevant topics, including:

- antibiotic resistance, including resistance mechanisms and the transfer of resistance;
- the supply and use of antibiotics in food animals;
- antimicrobial resistance in organisms of veterinary importance;

- antibiotic resistance in bacterial enteric pathogens;
- bacterial pathogens in animals which might be transmitted in food;
- the use of zinc oxide in the control of post-weaning diarrhoea in pigs;
- avoparcin; and
- the use of antimicrobials in aquaculture.

10. Written requests for information relevant to the Working Group's deliberations were sent to a broad spectrum of organisations in this country and abroad, including the farming, food, animal feed, fishing and pharmaceutical industries, public health and research organisations, representative bodies, academic institutions, veterinary bodies and consumer interest groups.

11. The Working Group is currently taking oral evidence and hopes to complete its work by the end of 1997. It is hoped that this will enable a report to go forward from the Group's parent body (the ACMSF) to the Government early in 1998.

Professor D L Georgala

Chairman, Advisory Committee on the Microbiological Safety of Food.

August 1997

**Memorandum by Professor S G B Amyes DSc, PhD, FRCPATH, FIBiol, University of Edinburgh,
and Dr Hilary-Kay Young, PhD, University of Dundee**

1. INTRODUCTION

1.1 The Department of Medical Microbiology of the University of Edinburgh is the largest university department in the subject in the whole of the United Kingdom. There is a large research section devoted to the study of antimicrobial resistance. This research team has published more than 250 papers on antimicrobial resistance and holds a number of research grants. This team works in close collaboration with the Department of Biological Sciences at the University of Dundee which provides the molecular biology input into the research initiatives.

1.2 We are pleased to have opportunity to respond to the invitation of the Subcommittee 1 of the Science and Technology Committee to submit evidence on resistance to antimicrobial agents. The rise of resistance is not a sudden development but has been a progressive increase over the past 25 years and, in this country, has particularly been associated with changes in surgical procedures during that time. The reason why we are in this apparent crisis is probably two-fold; firstly, there is still considerable complacency amongst prescribers, particularly in hospital, that the problems of resistance either do not exist or will be solved by the identification of new antibiotics by pharmaceutical companies; secondly, the surveillance procedures that we employ are completely inadequate for modern epidemiological purposes. Many practitioners and some diagnostic laboratories are not even aware of the problems that exist within their local area. There is no national database of resistance development and often there is no co-ordinated approach to examine the problem, much of the research is performed sporadically by interested individuals. The problem is certainly present and is likely to be more troublesome than the outbreaks of *Escherichia coli* O157 or the current number of reported cases of Creutzfeldt-Jakob Disease II. It is impossible to determine the number of patient deaths attributable to antibiotic resistance; the resources have never been provided to examine this. This information is, of course, highly sensitive and against the interests of hospital trust authorities either to divulge or even to examine it. The admission by a hospital that it has an antibiotic resistance problem, particularly if this leads to treatment failure, has the potential to attract litigation.

2. IDENTIFICATION OF THE PROBLEMS CAUSED BY RESISTANCE

2.1 There has been much discussion in the press in the last few years about the rise of the so-called "super-bugs"; however, little evidence and hard fact has been provided. We have examined resistance in the developed and the developing world. In the developing world, there is an urgent crisis in resistance development in community pathogens including, in some areas, *Salmonella typhi*, the causative agent of typhoid. Indeed, in some parts of the world, the problem of resistance is so bad that all the population carry resistance genes in their normal gut bacteria. It is impossible to comprehend how this situation can be controlled as it renders many antibiotics totally useless and there are certainly a large number of deaths directly attributable to antibiotic resistance. Interestingly, in many hospitals, resistance in developing countries is less of a problem than in the United Kingdom because the concentration of antibiotic usage is less and there are usually, but not always, fewer procedures requiring immunosuppression of the patients.

2.2 In the United Kingdom, the problems with resistance are still confined almost exclusively to hospitals. There is much debate about the emergence of multi-drug resistance tuberculosis and penicillin-resistant pneumococci but these pathogens are still very rare in this country and, whereas they may eventually pose a threat, there are immediate problems that require our urgent attention.

3. RESISTANCE PROBLEMS IN BRITISH HOSPITALS

3.1 The reality is that we appear to be moving in hospitals towards an era not just of multi-drug resistant bacteria but totally-resistant pathogens. The future of hospitals harbouring these bacteria is that certain procedures, particularly those that involve immunosuppression of the patient, will either have to be curtailed or risk assessments will have to be made and patients counselled so that they can judge whether the risk of untreatable infection is worth the potential benefit of surgery. We identify three hospital pathogens that fall into this category, they are vancomycin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and carbapenem-resistant *Acinetobacter baumannii* and identify *Klebsiella* species as a potential problem in the near future. This is not to say that these are the only totally-resistant bacteria, there are others such as *Stenotrophomonas maltophilia* but these are still not proven pathogens.

3.2 *Staphylococcus aureus*. The problems of methicillin-resistant *Staphylococcus aureus* (MRSA) are well-known and is particularly worrying because these pathogens can infect patients in all parts of a hospital. This organism is the single most problematic general hospital pathogen. So widespread is this problem that there have been ward closures in some hospitals because of the invasion of this pathogen. We have, however, remained relatively secure in the knowledge that we still had the glycopeptides (vancomycin and teicoplanin) to treat these organisms. Recent reports from Japan have demonstrated that MRSA can lose their susceptibility to the glycopeptides and become virtually impossible to treat with conventional antibiotics. If this problem comes to United Kingdom hospitals, we are going to face a control problem that could take a substantial part of the Health Budget to control.

3.3 *Enterococcus faecalis* and *Enterococcus faecium*. In the late 1980s and early 1990s, as transplantation became a more widely used procedure, the necessity to immunosuppress more patients becomes acute. These patients have little defence against bacterial infection without the blanket cover of antibiotics. This environment has provided an ideal opportunity for the enterococci to proliferate. These pathogens, predominantly *Enterococcus faecalis* and *Enterococcus faecium*, infect patients predominantly in the Intensive Care Units and, as they are exposed to more antibiotics, progressively acquire more resistance genes including resistance to the glycopeptides. This has resulted in a number of outbreaks in British hospitals. These are no longer treatable with conventional antibiotic therapy. In Edinburgh, we managed to eradicate an outbreak of vancomycin-resistant enterococci; this did require the very expensive introduction of barrier nursing techniques and the reduction of the availability of vancomycin from the hospital pharmacy. The vancomycin-resistant enterococci are now the second most common cause of infection in the Intensive Care Unit.

3.4 *Acinetobacter baumannii*. Twenty years ago, this bacterium was not considered to be a pathogen. It was largely sensitive to most antibiotics. It was even sensitive to ampicillin. The introduction of the second-generation cephalosporins initiated a rapid response and this bacterium rapidly became resistant. As each new antibiotic was introduced to combat it, the organism became resistant. Indeed it began to fill the vacuum left by other, more common bacteria which were largely eradicated by this successive antibacterial therapy. In Edinburgh, the bacterium was completely sensitive to the fluoroquinolones so these antibiotics were used to control. Within a year, 68 per cent of isolated strains had acquired resistance to it. The speed of this resistance acquisition is unprecedented. There are only two therapies that can still be used against contemporary *Acinetobacter baumannii*, carbapenems and sulbactam. Carbapenem resistance was first identified by us in Scotland in 1987 and is widely disseminated around the world as we have just reported in *The Lancet*. We have just identified the spread of an epidemic resistance gene bla_{ARI-2}, which confers resistance to all the carbapenems including imipenem and meropenem, that has spread from South America to the far East. These bacteria would normally be treatable with sulbactam. This poor β -lactam antibiotic is really a β -lactamase-inhibitor. It is active against *Acinetobacter baumannii* but is not significantly bactericidal. It is a poor drug to rely upon as a final defence. Unfortunately many of the strains resistant to carbapenems are resistant to sulbactam as well so they are effectively untreatable with antibiotics. Even if the bacteria in the United Kingdom were still sensitive to sulbactam, it would make little difference as the drug is not available for therapy in this country. *Acinetobacter baumannii* is the most problematic Gram-negative pathogen in Intensive Care Units. Like MRSA, *Acinetobacter baumannii* has also been responsible for the closure of wards.

3.5 *Klebsiella spp.* This genus is not yet totally untreatable but is currently causing havoc in some hospitals in the United Kingdom. It is usually controllable with the fluoroquinolones but resistance to these antimicrobials is emerging so the final control is likely to be the carbapenems. We have recently reported in *The Lancet* the emergence of carbapenem resistance.

4. SURVEILLANCE

4.1 The information produced by most diagnostic laboratories is insufficient to give an accurate picture of the emergence and spread of resistance. It is a system that is designed to provide treatment information for the individual patient rather than the broader epidemiological picture. The vast majority of laboratories cannot even distinguish whether the spread of resistance is due to clonal spread of a single bacterium or whether there is horizontal spread of resistance genes through the population. There is much in the literature about the horizontal spread by plasmid transmission of resistance from one strain to another; however, virtually no-one knows of the extent of plasmid carriage of resistance either within local areas or through the country as a whole. As well as plasmid epidemics, there may also be epidemics of transposons and even

integron elements. We simply do not know, in most cases, whether we are witnessing a few successful resistant bacteria spreading through the population or, as speculation often suggests, we are observing the rapid transmission of successful resistance genes. This information is absolutely crucial for the local therapy management of the outbreak.

4.2 Some epidemiological information should be provided by the reference laboratories, which currently take the most problematic strains from the network of diagnostic laboratories around the country. This information may but certainly may not be representative of what is happening around the country. This system of referral is often sporadic, there is not a single network of laboratories throughout the United Kingdom. Scotland is outside the jurisdiction of the Public Health Laboratory Service and has its own reference laboratories. In the United States, the Center for Disease Control has initiated a series of programmes that will pro-actively go into hospitals to examine all the strains responsible for certain infections. Only an approach such as this can give a true picture of emerging resistance.

4.3 Almost all surveillance data demonstrate that the only valid method to compare information from different centres is to perform the comparative tests in a single laboratory with well defined control. Comparison of data from different centres is often inaccurate and may lead to false conclusions. The corollary is that testing, especially for epidemiological reasons should be performed in as few laboratories as possible. This type of central testing might be a conflicting interest in a trust hospital infrastructure.

4.4 *Action 1:* The traditional diagnostic methods have failed to halt the emergence of resistance or even attempt to control it. There should be an immediate re-evaluation of the role of diagnostic laboratories and the reference laboratories. In Scotland, there should be a central reference facility sited within a single building as there is in England and Wales. The identification of resistance genes in clinical bacteria should be cross-referenced with those identified in animals so, in preference, these tests should be done by the same laboratory.

4.5 *Action 2:* New genetic and molecular biological techniques must be developed to identify and classify bacteria. Bacterial classification has been an area of much controversy and is largely based on a system of tests initiated on biochemical responses which were originally introduced in the early part of the century. We now know there is considerable variation with a so-called species and these variants may respond very differently to antibiotics. It is simply no longer adequate to use out-moded classification systems.

4.6 *Action 3:* Immediate measures should be introduced pro-actively to conduct a survey at crucial centres throughout the United Kingdom, making sure that the criteria for the isolation and identification of the bacteria are consistent. All strains are then sent to a central testing facility and so bacteria from different centres can then be compared directly. This type of study has usually been achieved only by the pharmaceutical industry. These are the only organisations willing to put money into such studies. Whereas the aims for such studies are admirable, they should be funded by bodies that have no vested interest in the result. Any study funded by an organisation, that is not independent, has the risk that the results may be presented in a favourable light for a particular drug or even unfavourable data might be excluded.

5. CONCLUDING COMMENTS

5.1 We are facing this problem because our current surveillance procedures have proved inadequate in the identification and control of antibiotic resistance. We must define what information we require and ensure that it is provided independently. We need to employ much more sophisticated molecular approaches, the technology is available and should be introduced. This information should be entered into a national database and should be available to prescribers. As resistance begins to increase in a local area, measures should be introduced to control it. If this means removal of antibiotics and barrier nursing, the high cost that this inevitably would generate might produce much more significant savings in the future.

20 December 1997

Supplementary Memorandum by the Association of Medical Microbiologists

Further to our evidence given to the Select Committee in October, this Association would like to submit further evidence in the form of this letter. Recent events have taken place and particularly one in the past two months which motivates us to do this.

It has come to our attention that Professor Mark Casewell has taken early retirement from his post at King's College Hospital and may well not be replaced. This follows the loss of a number of senior academic posts in clinical microbiology in the UK over the past decade, a trend which in our opinion has seriously damaged research endeavour in the more applied aspects of our discipline. The trend is almost certainly the consequence of the HEFC Research Assessment Exercise (RAE) which has laid greater value on the more fundamental aspects of research than those of a more practical and immediately applicable nature. While this is clearly laudable in terms of originality and long-term benefit it does put clinically orientated disciplines in a difficult position.

With regard to the particular problem of antibiotic resistance, research well rated by the RAE will undoubtedly make a great contribution to ameliorating the problem in the long term. We believe, however,

that we do not have the time to realise these benefits before there are serious consequences in British hospitals resulting from further developments in antibiotic resistance. It is only a matter of time measured in single figures of years before, in our opinion vancomycin in resistance MRSA reaches us for example.

What is urgently needed is research into the epidemiology of and control measures for antibiotic-resistant bacteria both in hospitals and the community. Much of such research needs to be done in hospitals and in laboratories servicing them and the community at large. Funding should be made available to do this on a large scale either via the HEFC or the DoH. However, such funding will not be maximally beneficial without skilled and experienced researchers in clinical microbiology who are able to make best use of it. It is important therefore that clinical research is somehow more favoured by the RAE or there will be more losses of the very staff with the capability to lead such research and who have the credibility to ensure the implementation of any changes in practice. It is unreasonable to expect most Consultant Medical Microbiologists to contribute substantially to research at a time when their numbers are static but their work load is increasing rapidly because of changes in medical practice and the increase of Consultant numbers in other specialities.

In conclusion, I hope that the Committee might consider stressing to the DoH, the HEFC and the CVCP the importance of applied research in the area of antibiotic resistance. It is this Association's opinion that increased knowledge leading to changes in clinical practice is urgently needed at least to maintain our present position before the benefits of more fundamental research can be realised.

Professor David S Reeves
President

15 December 1997

Memorandum by Professor GAJ Ayliffe, University of Birmingham

1. Antibiotic resistance is a problem in most countries of the world. A WHO symposium on "Monitoring and Management of Bacterial Resistance to Antimicrobial Agents" was held in Geneva in 1994 (Clinical Infectious Diseases 1997; 24 (Suppl 1).

Recommendations for the "Control of Methicillin-resistant *Staphylococcus aureus*" were published in 1996 (GAJ Ayliffe, WHO/EMC/LTS/96.1).

2. The prevention of cross-infection in hospitals is as important as control of use of antibiotics in the limiting of spread of antibiotic resistance.

3. Funding for research on the mode and prevention of spread of resistant organisms has been inadequate in recent years and many useful, often inexpensive, grants in this area have been rejected.

In the 1950s–80s, this country was a leader in research on properties of staphylococci and their spread, but units, such as the MRC Burns Unit in Birmingham, have been closed, or are now largely dependant on commercial contracts, as in the case of our own laboratory which was previously financed by the MRC and the Regional Health Authority.

4. Consideration should be given to planned studies on the mode of spread of MRSA and other resistant organisms and controlled trials on methods of prevention, possibly under the auspices of the MRC.

These opinions are my own, based on 40 years spent in research on hospital infection.

GAJ Ayliffe

Emeritus Professor of Medical Microbiology, University of Birmingham. Formerly Director of Hospital Infection Research Laboratory and WHO Collaborating Centre on Hospital Infection, Birmingham. Chairman of National Working Party on Methicillin-resistant *Staphylococcus aureus*.

27 September 1997

Memorandum by Dr B Bannister, Coppetts Wood Hospital

1. Coppetts Wood Hospital is a specialist referral centre for patients with all types of infection, whether contracted in the UK or overseas. I see about 1,200 inpatients and about 2,000 outpatients every calendar year.

2. The most frequently encountered multi-drug-resistant infectious disease at Coppetts Wood Hospital is tuberculosis. Approximately 50 patients per year are admitted with newly-diagnosed tuberculosis. 60–70 per cent of new tuberculosis cases have pulmonary tuberculosis and are therefore likely to be infectious. Altogether nine to 12 patients per year have resistant *Mycobacterium tuberculosis* infection, two or three of these patients have multi-drug-resistant *M tuberculosis*, the rest have resistance to Isoniazid or to Rifampicin. There does not seem to be an association between simple drug resistance and racial, or social groups. However, multi-drug-resistant tuberculosis has most frequently been identified in immigrants from the Kurdish regions of Turkey, and from some Central African countries. Although there are many immigrants and refugees from Somalia and Eritrea, multi-drug-resistant organisms do not seem to be a problem in

tuberculosis sufferers from these countries. We do not admit a significant number of HIV-positive patients with tuberculosis.

3. Because many of our admissions are referrals from the community, or from casualty departments, or are tertiary referrals of patients with community-acquired infections, the number of drug-resistant infections which we see with *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Enterococcus* species is negligible. In the last calendar year only one admission with staphylococcal infection out of a total of 30 was infected by a methicillin-resistant *Staphylococcus aureus*. This was a case of bacteraemia in a man recently discharged from a neighbouring acute hospital unit.

Dr B Bannister Sc FRCP

Consultant in Infectious and Tropical Diseases

12 September 1997

Memorandum by Dr J Bates, Worthing Hospital

There is increasing evidence to link the use of antibiotic growth promoters in animals with the emergence of multi-resistant bacteria in animals. There is some evidence to support the hypothesis that such multi-resistant organisms reach man via the food chain. In the case of antibiotic-resistant *Salmonella* and vancomycin-resistant enterococci, the evidence is highly suggestive.

SALMONELLA, CAMPYLOBACTER AND CIPROFLOXACIN RESISTANCE

The most convincing evidence relates to ciprofloxacin-resistant campylobacters and salmonellas. Ciprofloxacin was first licensed for human use in 1987 and still is an invaluable drug in the treatment of multi-resistant organisms. At launch, it was wrongly stated that acquired resistance to this antibiotic would not be a problem and use of the antibiotic was widely promoted. In 1993, enrofloxacin was licensed for use in the poultry industry and it is given to one day old chicks as a "therapeutic agent". It is structurally related to ciprofloxacin in that it is broken down to ciprofloxacin in the animal. Since enrofloxacin's introduction, data collected by the PHLS on *Salmonella typhimurium* and data from the Netherlands on campylobacters suggest that the emergence of ciprofloxacin-resistance in these organisms is secondary to antibiotic use in poultry. In my opinion this illustrates the general concerns that:

1. The widespread use of an antibiotic in both medical and veterinary fields has significantly diminished the therapeutic value of ciprofloxacin within 10 years.
2. There is a problem in the definition of antibiotics that might be used as therapeutic, prophylactic or growth promoting agent. Under the terms of the Swann Committee, antibiotics used in human medicine cannot be used as growth promoters. Since whole flocks can be prophylactically treated with antibiotics the impact of this on resistance may be comparable to their use as growth promoters and redefinitions are required for the non-essential use of antibiotics.
3. Little independent surveillance of resistance occurs when a new antibiotic is introduced for animal husbandry use or indeed for established antibiotics. The reason why growth promoters work is not fully established and even less is known of the continued effectiveness of the use of growth promoters. A lack of two way communication between medical and veterinary laboratories also compounds this problem. For example, it was only the finding of increasing resistance to ciprofloxacin in campylobacters which lead to research in the Netherlands which linked this phenomenon with animal husbandry use.
4. We need to know exactly what *classes* of antibiotics are being used (for example ciprofloxacin and enrofloxacin are both quinolones and one might have predicted that use of enrofloxacin in animals would lead to ciprofloxacin resistance), how much is being used per kilogram weight compared to human use, and for what animals.

VANCOMYCIN-RESISTANT ENTEROCOCCI

We are entering an era where we have multi-resistant organisms for which we do not have effective antibiotics to treat human infections, for example serious infections caused by vancomycin-resistant enterococci. The resistance mechanism of vancomycin is via a mobile piece of DNA, a transposon.

The transposon carrying the resistance gene is known to be readily transmissible with and between species. Avoparcin is an antibiotic used as a growth promoter in poultry and pigs and has been widely used throughout the EC since 1975. It is of the same antibiotic class as vancomycin and demonstrates cross resistance with it. Use of these antibiotics probably select for this resistant gene and preliminary data from the Netherlands show transposons from human and animal derived vancomycin-resistant enterococci to be indistinguishable (ie suggesting there to be an epidemic at a transposon rather than organismal level).

Vancomycin is a valuable antibiotic in human medicine for the treatment of infections like those caused by methicillin-resistant *Staphylococcus aureus*, MRSA. If the vancomycin-resistant gene were to transfer to

a pathogenic organism like MRSA (as has been done in the laboratory) this would transport us back to the situation last seen in the pre-antibiotic era.

Critics of this argument may say that we do not have 100 per cent proof that vancomycin-resistance is being transferred via the food chain and highlight their case by referring to the USA where vancomycin-resistance enterococci are a major clinical problem despite avoparcin never having been licensed for animal husbandry use. However, the use of vancomycin in the USA by far exceeds the usage of this antibiotic in Europe leading to the possibility that resistance arose independently from the selective pressure of excessive *human* use.

One must question the need to wait for absolute proof when the practice of using avoparcin as a growth promoter may compromise the value of an antibiotic as precious as vancomycin. Bacteria do not respect the artificial barrier which separates human from veterinary medicine. Some bacteria are able to cross species barriers and will be influenced by the selective pressures of antibiotics whatever the source. We need to look critically at the non-essential use of antibiotics in animal husbandry especially with those antibiotics which show cross resistance to important human therapeutic agents. However this scope may have to be widened because, as we search for newer antibiotics to combat ever increasing resistant human pathogens, we may have to fall back onto existing classes of antibiotics which are not presently used in human medicine but are used in animal husbandry. An important example of this is a new antibiotic called synergid awaiting licence for the treatment of infections caused by vancomycin-resistant enterococci. This antibiotic is structurally related to the growth promoter, virginomycin. Evidence emerging from the UK, Germany and the Netherlands shows that resistance to synergid in clinical strains already exists despite the fact that this antibiotic has hardly been used in human medicine. This finding can be explained by the use of virginiamycin as a growth promoter.

Memorandum by the Biotechnology and Biological Sciences Research Council

(i) BBSRC supports fundamental science relevant to the enquiry on the genetics, biochemistry and physiology of bacteria, viruses and parasites and on the epidemiology and diagnosis of infectious diseases which underpins work on antibiotic resistance, pathogenesis and immunity. More specifically, BBSRC has interests in (a) those organisms that cause disease in farmed animals, treatment of such infections with antibiotics, prevention of disease through the use of vaccines and the transfer of resistance characteristics to humans from handling animals with antibiotic resistant organisms and (b) the microbiological safety of food whether from potential disease causing organisms contaminating food or foods which purposefully contain microbes as part of the production process. One example of the latter would be the lactic acid bacteria which are a member of the enterococcus genus. These bacteria are used widely in dairy fermentations and are being promoted as probiotics for human consumption as live cultures. Other members of the enterococcus genus are of medical importance in nosocomial infections and exchange of genetic material, including that coding for antibiotic resistance, between members of this group of bacteria is well recognised. Transmission of antibiotic resistance by either route would have serious consequences.

(ii) This section is not applicable to BBSRC.

(iii) BBSRC supports research into the discovery of new drugs, the mode of action of antibiotics and the factors involved in antibiotic production. Identification of the genes coding for naturally produced antibiotics and the genetics of the control of antibiotic production continue to be important areas for support. BBSRC has recently initiated a programme to sequence the whole genome of *Streptomyces coelicolor*, which is a member of an important group of microbes which make almost two-thirds of all known natural antibiotics and which have provided the majority of new antibiotics in the past 50 years. These studies will allow the genetic manipulation of antibiotic producing strains for improved production of the natural molecule and for the production of novel compounds by genetic modification. Studies at the molecular level of antibiotic molecules, their cellular targets and complexes formed between are leading to the rational design of novel synthetic molecules which will be required to counter the appearance of pathogens resistant to current antibiotic. BBSRC also supports work which enables the discoveries made in the laboratory to be transferred to the production of antibiotics/drugs in industrial settings. These studies are by necessity multidisciplinary involving molecular biologists, structural biologists, microbial physiologists, chemists and engineers. BBSRC funded studies on the identification of virulence factors associated with pathogens and their antigenic composition, understanding how the immune system responds to infectious agents and the immune mechanisms responsible for disease resistance will open up the prospects for vaccination to many infectious diseases and therefore reduce the need for antibiotic use.

(iv) The role of Government through the Research Councils (and Funding Councils) is to ensure the strength of the science base by supporting underpinning research so as to be able to react to existing and unforeseen developments in this, and other, areas. As described in (i) above BBSRC supports a wide range of basic research which is essential for responding to current and future problems regarding resistance to antimicrobial agents. Current priorities of BBSRC include increased provision for structural biology research, genome analysis of agriculturally important species and genome sequencing of bacteria relevant to BBSRC's mission. Each of these topics are highly relevant to the area under scrutiny by the House of Lords S & T Committee. In future, Council is likely to develop other research priorities which would also be relevant to the subject such as microbial physiology, immunity to infectious diseases, mechanisms of bacterial evolution, etc.

Memorandum by the British Embassy in Tokyo**RESISTANCE TO ANTIMICROBIAL AGENTS IN THE JAPANESE POPULATION****INTRODUCTION**

The following is a brief report on the presence of drug resistant bacteria in Japan and the efforts being made to arrest the spread of infectious disease.

The emergence of multi drug resistant bacteria such as methicillin-resistant staphylococcus aureus (MRSA) has become a serious concern in cases of hospital acquired infection. The presence of multi-drug resistant Gram-negative bacteria is an increasing trend across the world and is a trend from which Japan is by no means isolated.

CURRENT STATE OF DRUG RESISTANT BACTERIA

The use, pro-rata, of antibiotics and antimicrobial agents in Japan is higher than that in either Europe or the United States. Increasingly in Japan the system for remunerating doctors has led to newly developed "wide-range type" antimicrobial drugs being administered in favour of existing drugs with proven efficacy; the corollary of which is a prevalence of multi-drug resistant bacteria, of types not yet emerged in Europe or the United States. Gram-negative bacillus able to resist all beta-lactam drugs and strains of bacteria, resistant not only to beta-lactams, but to aminoglycoside and the New-quinolone families of drugs are now evidence in Japan. However, whilst the spread of Vancomycin resistant enterococcus (VRE) has become a serious concern in Europe and the United States, through its ability to lower immunity in organ transplant patients, patients with blood related diseases and those in Intensive Care (IC), Japan has only one reported case of VRE. In the process of combating MRSA, Japan have lagged behind Europe and the United States in administering Vancomycin; thus to date avoiding the widespread development of VRE. The emergence of VRE has nevertheless awoken the Ministry of Health and Welfare (MHW) to the potential for increasingly widespread resistance to antimicrobial agents and to the possible serious effects on the Japanese medical system. Their response was to convene a meeting of experts to report on measures to be taken to deal with the rise in drug resistant bacteria ("Expert Meeting Concerning Measures for Drug Resistant Bacteria").

Newly developed antimicrobial agents are administered in a wide range of circumstances, including, for the control of the common cold and prevention of infection after routine operations. A lack of understanding of MRSA has resulted in inappropriate treatment of carriers, whether or not they have displayed symptoms. Access to certain medical facilities has been limited and unnecessary administration of antimicrobial agents carried out.

Listed below are the major bacteria having acquired resistance:

- MRSA;
- PRSP (Penicillin resistant staphylococcal pneumonia);
- Cephalosporin resistant Gram-negative bacillus;
- Gram-negative bacillus resisting beta-lactam inhibitor;
- New-quinolone-resistant bacteria;
- Aminoglycoside resistant bacteria; and
- Drug resistant mycobacterium tuberculosis.

MEASURES TO COUNTERACT DRUG RESISTANT BACTERIA

At the direction of the MHW medical "centres" have since 1991 established measures to stem the spread of hospital acquired infections. Initiatives have been developed to educate medical staff in ways of preventing the spread of infection, and where infection has occurred, training them how to deal with it. As a result 98.4 per cent of hospitals with more than 500 beds have set up committees to take measures to prevent hospital acquired infection.

Since 1992 the Pharmaceutical Bureau of the MHW have conducted nationwide surveys into the "current state of sensitivity of antibiotic agents". Covering 500 medical institutions, the studies examine the state of antibiotic's efficacy in controlling infection. In one such survey, up to a million samples were tested over a two week period. Nevertheless, this data is not sufficient for clinical purposes. A more statistically valid surveillance system, looking at individual patients, their illnesses and the effects of dosing regimes on resistance has therefore been introduced.

The measures to address MRSA are considered to have been successful, with the number of recorded cases having fallen. However, the true extent of the problem remains unknown.

In recognising the new threat from the emergence of VRE, the MHW have established a further three year programme involving the National Infectious Diseases Research Centre and hospitals, monitoring the incidence of widening resistance to antibacterial agents. A parallel group will evaluate the resistance to infection to drugs.

Although Japan is experiencing a decreasing trend in the administering of antibiotics, opinion remains divided on the most effective timing for the use of antibiotics and no advice has yet been given by the MHW as to what is appropriate use. It is however recognised that once agreed upon, the promotion of the correct use of antimicrobial agents amongst doctors and pharmacists will play a central role in delaying the emergence of drug resistant bacteria.

Efforts by drug companies to deal with such problems are generally undertaken unilaterally and it is likely to be three years before substantive recommendations dealing with the spread of multi-drug resistant bacteria are brought forward by the MHW.

Chris Stuart

First Secretary, Science and Technology

8 November 1997

Memorandum by the British Medical Association

The British Medical Association welcomes the Science and Technology Committee Enquiry into resistance to antimicrobial agents and wishes to submit the following evidence.

INTRODUCTION

1. Over the last three decades there has been an ever increasing rise in the use of, and dependence on, antimicrobial agents in the treatment of infectious diseases such as pneumonia, meningitis and tuberculosis. However, a global increase in resistance to antimicrobial drugs is emerging, including the development of bacterial strains resistant to all available antibacterial agents, leading to an enormous public health problem and a potential crisis.

2. One of the main reasons advocated for the development of antimicrobial resistance is the over-use and abuse of antibiotics. Antibiotic misuse is common and studies have suggested that up to 70 per cent of treatment courses are unnecessary or inappropriate. Therapy is often unnecessarily prolonged and prophylaxis is often inappropriate or given at the wrong time. The problems of antibiotic resistance are compounded as a result and resistant organisms are being easily transmitted between human hosts, as is the case with current epidemic strains of MRSA. Consequences of resistance include higher mortality and greater morbidity, such as neurological damage in children from meningitis not recognised as resistant to first line drugs. Infections with organisms resistant to antimicrobial agents lead to longer hospitalisation and increased health costs.

CURRENT SITUATION OF ANTIMICROBIAL RESISTANCE IN THE UK

3. The following text details the major infectious diseases and the extent and trends of antimicrobial resistance.

Tuberculosis

4. Resistance to at least two of the front line anti-TB drugs is now known—rifampicin and isoniazid. These two drugs are essential for most initial or short course treatment regimes, and strains of TB resistant to them soon develop resistance to other drugs also. Resistance to antimicrobial agents in the treatment of tuberculosis is thought to be the result of spontaneous chromosomal mutations in the organism when a single drug is used. Other reasons advanced for the development of multi-drug resistance to TB in the West include:

- failure of patients to comply with drug regimes leading to inadequate therapy and resistant mutants;
- deterioration of public health services directed towards the control of TB;
- inadequate training of health care workers in the diagnosis, treatment and control of TB;
- laboratory delays in the detection and sensitivity testing of TB;
- addition of single drugs to failing treatment regimes; and
- an increase in the number of individuals at high risk of acquiring and disseminating TB, related to HIV, poverty and homelessness.

5. Mortality rates in multi-drug resistant TB are high in all patients and especially those with HIV. The single most important factor in the prevention of further emergence of MDR-TB is probably the reintroduction of supervised observed therapy for a patient taking a course of antibiotics.

Hospital Infections

Methicillin-resistant *Staphylococcus aureus* (MRSA).

6. MRSA was first detected sporadically in Europe in 1961 and in the last 20 years the proportion of MRSA in hospitals has fluctuated in European countries from 1-2 per cent or less in N Europe to 30-40 per cent in Spain, France and Italy.¹

7. MRSA has become a major problem of multiple drug resistant hospital infection in the 1990s. Methicillin resistant strains of *S. aureus* are also resistant to oxacillin, nafcillin, cephalosporins, and imipenem and frequently resistant to most other antibiotics such as erythromycin and clindamycin, that are sometimes used to treat staphylococcal infections. Many strains of MRSA remain sensitive only to the glycopeptides, vancomycin and teicoplanin but if MRSA were to acquire vancomycin resistance from enterococci, serious untreatable staphylococcal infection would result.

8. An outbreak of MRSA was reported in a hospital in Melbourne, Australia in the late 1970s, early 1980s and infection control staff traced the infection to inanimate objects such as linen, washing facilities and also some personnel. The strain was resistant to all traditional first line antibiotics and had large implications. Stringent infection control procedures are therefore essential in preventing the spread of MRSA in health care facilities. Continued vigilance, a strict enforcement of preventative measures, and restricted use of glycopeptides both in human beings and animals represent our best response to the spread of multi-resistant cocci worldwide.

Pneumonia

9. Pneumonia is mainly caused by the pneumococcus *Streptococcus pneumoniae*. The primacy of the pneumococcus in pneumonia is emphasised by the British Thoracic Society guidelines which are in widespread use.² The guidelines state that, whatever antibiotics are used in pneumonia, it is essential that an agent active against the pneumococcus is included. Despite the availability and administration of appropriate antibiotics, mortality and morbidity still occurs from pneumonia. A vaccine has been available for about 17 years but is not in widespread use. The increasing emergence of resistance of the pneumococcus to penicillin is a matter of concern, although it has not arisen as a problem yet in the UK.^{3,4}

Gonorrhoea

10. Previously, penicillin offered an easy cure, but some bacteria have now become resistant to this first line antibiotic. This has necessitated a change to other agents, such as tetracycline, traditionally the second line agent for patients allergic to penicillin and also the newer cephalosporins, spectinomycin or the quinolones, with clear financial implications for the newer agents. Since the incidence of resistance varies between localities, a policy for treatment should be based on knowledge of the local resistance pattern.⁵

Salmonella

11. In Britain, multiple resistance in *Salmonella typhimurium* doubled in isolates between 1981 and 1990 and quadrupled in bovine isolates. In contrast, multiple resistance was uncommon in *Salmonella enteridis* which is usually derived from poultry in which there is less use of antibiotics in feeds than in cattle. The disease reporting system in England and Wales has revealed a 10 fold increase in the number of human cases of multi-drug resistant *Salmonella typhimurium* DT104 in the six year period 1990-96, going from 300 to 3,500 cases per year. More than 55 per cent of cases of this bacteria in humans were caused by the multi-drug resistant DT104. There is a body of evidence in the scientific literature suggesting the possibility that some of these strains of drugs may have emerged due to the use of antibiotics in intensive animal husbandry.

PRESCRIPTION AND USE OF ANTIBIOTICS

12. Murray (1994)⁶ states that although the emergence of resistance may be the inevitable result of the use of antimicrobial agents, there is clear evidence that this need not occur to the degree that it does now. A study by Weis et al (1994)⁷ found differing rates of resistance with different therapeutic approaches to the treatment of tuberculosis. Many studies show that enforcement of infection-control measures in hospitals, often in combination with reductions in antibiotic use, can decrease the rates of resistance.

13. The UK may be somewhat ahead of some other countries in that antimicrobial agents are available only on prescription, and clear guidance is provided on drug labels that the course should be finished. In addition, we have in place a very good surveillance system for the emergence of antimicrobial resistant bacterial strains through the Public Health Laboratory Service for England and Wales. All known incidences of diseases such as those listed above and any other antimicrobial resistant bacteria should be reported to the Communicable Disease Centre of the PHLS but this is unfortunately not mandatory. The installation in laboratories of the Epinet/Cosurv system for electronic reporting has been very helpful in enabling us to do this. One project currently at an early stage of development led by the PHLS is NINSS (Nosocomial Infection

National Surveillance Scheme). This attempts to address the lack of “denominator” data in current surveillance but one problem that can occur is the poor quality of hospital patient information systems, which are the source of such data.

14. The Department of Health has issued new guidelines for the prevention and control of multi-drug resistant tuberculosis in hospitals as increased incidences of this disease emerge. Effective infection control measures are of great importance to the prevention of cross infection and the BMA has been active in advising individual doctors and NHS management on infection control, through the publication of reports and codes of practice. The BMA’s materials on bloodborne infections have been utilised by government departments and external agencies in advising hospitals and doctors on effective infection control policies.

15. In 1996, the BMA commented on the World Medical Association (WMA) statement on resistance to antimicrobial agents emphasising the importance of public education in advising patients that they should not always expect antibiotics to be prescribed when attending their medical practitioners. In addition, it was suggested that information about antimicrobial resistance could be provided by pharmaceutical companies when promoting antibiotics warning that incomplete or inappropriate treatment may not only lead to a recurrence of illness in the individual, but is also the main cause of the development of drug resistant strains of tuberculosis.

FUTURE OF ANTIMICROBIAL AGENTS

16. As there are now few therapeutic alternatives to replace antibiotics in the fight against antimicrobial resistant infections and diseases, there is an urgent need for a change in attitudes towards the use of our current range of antibiotics. To control the further development and spread of antibiotic resistance, it is essential to reduce unnecessary antibiotic usage and prevent cross infection with multi-drug resistant pathogens. A recent paper in the British Medical Journal reported an open randomised trial of prescribing strategies in managing sore throat. The paper concluded that prescribing antibiotics for sore throats does not reduce the extent and duration of the symptoms compared to those who received delayed or no antibiotic prescription. The paper also concluded that prescribing antibiotics enhances belief in antibiotics and the intention to consult.⁸ Prescribing practice and patient education are therefore essential in reducing the use and abuse of antibiotics and the BMA recommends that the Government provides funding for this purpose.

17. In settings where the rate of transmission of resistant organisms is high, such as hospitals and day care centres, the rate of transmission of pathogenic organisms and thus the incidence of disease also tend to be high, which in turn leads to greater use of antibiotics. Strategies must therefore address not only heavy use but also the ease in which the diseases may spread.

18. Recent news in the British Medical Journal reports that researchers have developed a genetic engineering technique that allows drug resistant bacteria to be rendered drug sensitive. This may prove to be a cheaper method of negating antibiotic resistance than the current approach of developing new drugs.⁹

19. Research must be encouraged to develop new drugs, but the high cost of the research and development process and obtaining patents is a significant barrier to many researchers and organisations. Resources are also needed for research into the efficacy of antibiotics as drug companies may not be willing to pay for research that might prove their product ineffective. We therefore recommend that the Government provide funding and subsidies for such projects.

20. Both the World Health Organisation and the World Medical Association have issued statements on their future policies for the control of antimicrobial resistance (see Appendix I and II attached). The BMA supports the recommendations of the WMA and the WHO.

BMA RECOMMENDATIONS

21. To overcome the problem of antimicrobial resistance, attention must be focused on societal issues that determine how these drugs are used and there is a need to move to more selective and rational use of antimicrobial drugs in practices and hospitals.

22. The BMA has taken a number of actions in relation to the evidence for an increase in antibiotic resistance within the UK and worldwide. The BMA has raised with government the need to prioritise research on antibiotic resistance and suggested that one area where there is a need for concentrated research is that of infectious diseases due to the development of multi-drug resistance by many organisms. The BMA outlined that this would present significant difficulties for the health service in the future. The responsibility of this work should not lie entirely with the health service and there should be an obligation upon pharmaceutical companies to ensure the availability of drugs for diseases in which there is a social need. There is also an urgent need for research into the development of new and effective mechanisms of dealing with infectious disease. Globally and within the UK, rates of infectious disease are increasing and the resistance of many organisms, particularly those causing common hospital infections, make this a pressing area for research.

23. The BMA is a signatory to the World Medical Association statement on resistance to antimicrobial agents. The final recommendation relates to the use of antimicrobial agents as feed additives for animals. This recommendation has been included due to the medical profession’s concerns regarding the possible transfer

of antibiotic resistance to humans through the use of such feed additives. The antibiotic avoparcin, used to promote growth in animals has recently been banned by the European Union on the grounds that it might encourage the spread of drug resistance from farms to hospitals.

24. The BMA recommend that:

- that the health profession should be educated in the prescribing, dispensing and consumption of antibiotics in relation to resistance and that this should be funded by the Government;
- that patients should be educated to not always expect antibiotics and to emphasise the importance of completing a full course when they are prescribed and that this should be funded by the Government;
- the Government should introduce more comprehensive infection control guidelines for the prevention and control of hospital acquired infections and provide more funding;
- the Government should investigate the introduction of legislation requiring changes in the management and practice of agriculture and the use of performance enhancing antibiotics in agriculture;
- the NHS should agree infection control standards with managers of elderly/residential homes where there are high incidences of community acquired infections;
- that the PHLS, as an effective surveillance service on the emergence of antimicrobial resistant strains of bacteria, be provided with more funds to increase their service;
- that the reporting of all known incidences of antimicrobial resistance to the Communicable Disease Centre of the PHLS should be made mandatory;
- that the pharmaceutical industry, in cooperation with the research community, be actively encouraged, and funded by the Government where necessary, to research and develop new antibiotics and vaccines against microbial diseases;
- that the pharmaceutical companies should provide information about antimicrobial resistance when promoting antibiotics;
- that the research community consider the role of complementary medicine in the treatment of microbial diseases;
- that supervised observed therapy should be reintroduced for patients taking a course of antibiotics for the treatment of tuberculosis;
- that a policy for the treatment of antimicrobial resistant strains of gonorrhea should be based on knowledge of the local resistance pattern.

I hope that you find these comments of help and I look forward to hearing of the outcome of your enquiry on this subject.

M J Lowe

Deputy Secretary

26 September 1997

REFERENCES

1. Michel M, Gutmann L. *Methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci: therapeutic realities and possibilities*. *Lancet* 1997;349:1901-06.
2. Anonymous. Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. The British Thoracic Society. *British Journal of Hospital Medicine*. 1993;49(5):346-50.
3. Goldsmith CE, Moore JE, Murphy PG. Prevalence of antibiotic resistance in pneumococci and Northern Ireland. *British Medical Journal*. 1996;312(7044):1454-6.
4. Lambert HP. Managing patients with an absent or dysfunctional spleen. Guidelines do not discuss resistance to antibiotics among pneumococci. *British Medical Journal*. 1996;312(7028):430-4.
5. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary, Number 32*. London: The British Medical Association and The Pharmaceutical Press, 1996.
6. Murray BE. *Can Antibiotic Resistance be Controlled?* *New England Journal of Medicine* 1994;330:1229-30.
7. Weis SE, Slocum PC, Blais FX, et al. *The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis*. *New England Journal of Medicine*. 1997;330:1179-84.
8. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. *Open randomised trial of prescribing strategies in managing sore throat*. *British Medical Journal* 1997;314(7082):722-7.
9. Abbasi K. *Genetic engineering reverses antibiotic resistance*. *British Medical Journal* 1997;315(7105):385.

APPENDIX I

WMA RECOMMENDATIONS:

- The World Medical Association and its member national medical associations should encourage the World Health Organisation (WHO) and other individual governments to cooperate with and enhance the effectiveness of the WHO's global network of antimicrobial resistance surveillance.
- National medical associations should encourage their governments to fund more basic and applied research directed toward the development of innovative antimicrobial agents and vaccines, and on the appropriate and safe use of such therapeutic tools.
- The pharmaceutical industry should be encouraged to pursue research and development programs leading to the availability of innovative antimicrobial agents and vaccines.
- National medical associations should urge their governments to require antimicrobial agents to be available only through prescription by licenced qualified health care and veterinary professionals.
- National medical associations should encourage medical schools and continuing medical education programs to educate physicians about appropriate use of antimicrobial agents.
- Physicians, especially trained in infectious diseases and clinical microbiology, should assume leadership roles in their local hospitals and communities regarding appropriate antimicrobial agent usage and antimicrobial resistance prevention and control programs.
- Physicians should raise awareness amongst their patients of their antimicrobial therapy, the risks and benefits, the importance of compliance with the prescribed regimen, and the problem of antimicrobial resistance.
- Governments, medical associations, and physicians should educate the public in the appropriate use of antimicrobial agents and increase the awareness of the problem of antimicrobial resistance.
- National medical associations in collaboration with veterinary authorities should encourage their governments to restrict the use of antimicrobial agents as feed additives for animals strictly to those which are not used for humans.

APPENDIX II

WHO RECOMMENDATIONS:

- Establish policies to control the availability of antibiotics and to promote their appropriate use.
- Establish methods and setting standards for evaluation of hospital based infection and antibiotic resistance prevention and control programmes.
- Establish self sustaining models for prevention and control of hospital acquired infections in designated collaborating hospitals that will provide training and expert consultation for relevant personnel.
- Global expansion of the network of antimicrobial resistance surveillance activities through the WHO computerised system WHONET.
- Extend existing collaboration and partnerships in this area to include international agencies, government and non government organisations, academia and the pharmaceutical industry.
- Encourage basic research towards new approaches to the development of antimicrobials.

Memorandum by the British Pharmacological Society

1. Infections are the most frequent reasons for patients to consult a general practitioner,¹ and often result in the prescribing of an antibiotic.² Antibiotic prescribing in general practice is often considered inappropriate, and its volume excessive.^{3,4} In particular, antibiotics are widely prescribed for poorly defined respiratory tract symptoms that may well be viral in origin.² In these cases, the use of antibiotics is of questionable benefit, may be detrimental to the patient, and may contribute to the increasing problem of bacterial resistance.² Recent new evidence from Finland has illustrated the growth of resistance to the antibiotic erythromycin associated with its heavy use, and the subsequent decline in resistance when its use was curtailed⁵.

2. Research has demonstrated the contribution of "environmental" factors such as practice demographics,^{1,7} morbidity⁸ and socio-economic status⁸ to prescribing variation. Doctor dependent factors, such as the extent of the doctor's postgraduate education,^{9,10} the practice's response to financial constraints such as fundholding prescribing budgets¹¹ and how well the practice is managed and organised may also contribute to this variation. These factors are likely to be inter-dependent.

3. Similarly, there is inter-practice variation in antibiotic prescribing volume and cost,^{3,12} which may also be due to the same factors. Some further variation may be due to differences in patients' expectations of a prescription for an antibiotic,¹² or to differences in doctors' perceptions of those expectations.¹³ In studying

these variations in antibiotic prescribing, the age and sex composition of a practice might be particularly important, since children and younger women tend to consult more frequently for infections.¹

4. Even allowing for such variations it can be shown that antibiotic prescribing is related to practice characteristics: practices with lower levels of deprivation prescribe fewer antibiotics than those with higher levels, training practices prescribe less than non-training practices, and multiple partner practices less than single-handed practices (T Walley, unpublished data). These factors are not mutually exclusive: training practices and larger practices tend to operate in less deprived areas.

5. This may in part be related to the rate of consultation, which is higher in more deprived areas,^{8,14} either because of morbidity or for other reasons. Sore throat is a common reason for GP consultation and whether an antibiotic is prescribed depends on many factors as discussed above.¹⁵ It has recently been shown¹⁶ that sore throats can be equally well treated without antibiotics (already recognised) and with another advantage: the patient becomes more self-reliant and is more inclined to self-manage such minor complaints in the future, while the use of antibiotics reinforces the prescription seeking even if unnecessary.

6. Recent NHS reforms such as GP fundholding have encouraged the use of less expensive antibiotics but the rate of utilisation has remained unchanged (T Walley, unpublished).

7. To improve the use of antibiotics and diminish the risks of resistance, the following measures might be considered:

- (a) Establishment of local or even national formularies which can be guided by the patterns of antibiotic resistance locally. The formulary can be modified as resistance patterns vary or even selected antibiotics rotated to try to reduce the development of resistance.
- (b) Some powers to encourage the use of the selected formulary should be given to the local health authorities: while not wishing to impede the right of the doctor to select the most appropriate antibiotic for his patient, there is a need to limit the range of antibiotics widely used. A scheme of antibiotic audit with identification of those prescribing widely outside the guidelines to his/her peers may be adequate for this and could be easily undertaken.
- (c) Advertising of inappropriate antibiotics or unnecessarily powerful antibiotics for minor indications is common, and undoubtedly misleads doctors. This should be strongly discouraged.
- (d) Education of both the general public and health care professionals in the proper use of antibiotics is needed; the message used in public education campaigns in Northern Ireland "there isn't a pill for every ill" well summarises the messages required.

T Walley

27 September 1997

REFERENCES

- 1 McCormick A, Fleming D, Charlton J. Morbidity statistics from general practice. Fourth national study 1991-92. London: HMSO, 1995.
- 2 Davey P, Rutherford D, Graham B et al. Repeat consultations after antibiotic prescribing for respiratory infection: a study in one general practice. *Br J Gen Pract* 1994;44:509-13.
- 3 Howie JGR, Richardson IM, Gill G, Durno D. Respiratory illness and antibiotic use in general practice. *J R Coll Gen Pract* 1971;21:657-63.
- 4 Marsh GN. 'Curing' minor illness in general practice. *BMJ* 1977;2:1267-9.
- 5 New Eng J Med July 1997.
- 6 Wilson RPH, Hatcher J, Barton SB, Walley T. Influences of practice characteristics on prescribing in fundholding and non-fundholding general practices. *BMJ* 1996;313:595-9.
- 7 Roberts SJ, Harris CM. Age, sex, and temporary resident originated prescribing units (ASTRO-PU): new weightings for analysing prescribing of general practices in England. *BMJ* 1993;307:485-8.
- 8 Worral A, Rea N, Ben-Shlomo Y. Counting the cost of social disadvantage in primary care: retrospective analysis of patient data. *BMJ* 1997;314:38-42.
- 9 Hemminki E. Review of literature on the factors affecting drug prescribing. *Soc, Sci & Med* 1975;9:111-5.
- 10 Taylor RJ. Prescribing costs and patterns of prescribing in general practice. *J R Coll Gen Pract* 1978;28:531-5.
- 11 Wilson RPH, Buchan I, Walley T. Alterations in prescribing by general practitioner fundholders: an observational study. *BMJ* 1995;311:1347-50.
- 12 Gonzales R, Sande M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis? *Lancet* 1995;345:665.
- 13 Britton N. Patients' demands for prescriptions in primary care. *BMJ* 1995;310:1084-5.

- 14 McGovack H, Wilson Davis K, Milligan E. Completing the triangle—Relationships between practice demography, general practitioner workload and prescribing. *Pharmacoepidemiology and Drug Safety* 1993;2:133-43.
- 15 Pitts J, Vincent S. What influences doctors' prescribing? Sore throats revisited. *J R Coll Gen Pract* 1989;39:65-6.
- 16 Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997;314:722-7.

Memorandum by the British Poultry Meat Federation

ANTIBIOTIC USE IN POULTRY REARING

INTRODUCTION

1. This submission sets out the rationale for the use of antibiotics in poultry reared for meat production. It considers the constraints on the use of specific types of antibiotics to ensure that they do not contribute significantly to the level of resistant bacteria in the human population. It also addresses the issue of the risk of antibiotic resistant bacteria of poultry origin infecting people or transmitting their resistance to other bacteria causing human infections.

2. Only antibacterials specifically authorised under EU and UK regulations are used in UK poultry flocks. These are administered at the dose rates prescribed on the data sheets and withholding periods are strictly observed. New scientific knowledge, bacterial mutations, or increasing numbers of immune-compromised people may require that the use of previously acceptable antibiotics in agriculture be modified or even discontinued. However, these factors need to be balanced against the positive health benefits deriving from supplying the bulk of the population, including the less affluent, with a wholesome, nutritious and affordable food. The poultry meat industry accepts that the consumer is entitled to expect that the food it produces is safe.

RATIONALE FOR THE USE OF ANTIBIOTICS IN POULTRY

3. Poultry, from time to time, become ill with bacterial infections and it is imperative from a welfare point of view that sick birds are treated to avoid suffering. These infections occur whether the birds are in relatively small populations on range or in open sheds, or on larger farms in closed houses, but the type of illness may differ depending on the husbandry system. The overall incidence of bacterial infections, however, may not vary significantly between one commercial husbandry system or another.

4. Given the large number of birds, even on relatively small holdings, mass oral medication is the only practical method of treatment of birds in most cases. Herding and picking up birds to medicate them individually when illness is present in a flock is stressful and will often exacerbate the situation and is therefore avoided. For mass oral medication to succeed birds must be fit enough not only to reach feed and water but to eat and drink if they are to receive the medication. This necessitates prompt action at the onset of infection if health and welfare are to be safeguarded.

THERAPEUTIC ANTIBIOTIC USE

5. Therapeutic treatment is applied when birds in a flock are either clinically ill and/or dying as a result of a bacterial infection. It is standard practice to identify the bacteria involved and carry out an antibiotic sensitivity test on them prior to or concurrently with any treatment. The entire flock is then treated with the most appropriate antibiotic. Only officially authorised antibiotics supplied or prescribed by a Veterinarian can be administered.

PROPHYLACTIC ANTIBIOTIC USE

6. This is a much misunderstood area. Prophylactic medication is only used in respect of specific cases of predicted disease infection. The poultry industry monitors breeding stock on a regular basis for certain infections, particularly those which are transmitted from the breeding hen via the egg to the chicken. Depending on the type of infection, the disease may manifest itself at day-old or some later age which can usually be predicted with some accuracy.

7. Rather than wait for the birds to become clinically ill and possibly unable to eat or drink properly before being treated, they are medicated at the time when the infection is predicted to occur. This has the advantage of preventing suffering in the bird and reducing the amount of antibiotic required to ensure effective treatment. As with therapeutic usage, only authorised antibiotics supplied or prescribed by a Veterinarian can be used.

DIGESTIVE ENHANCERS

8. Digestive enhancers, sometimes referred to as “growth promoters”, are types of antibacterials reserved only for animal use which enable the bird to digest its feed more efficiently by acting on the gut flora. There is a view that digestive enhancers are used purely for economic reasons and therefore, however remote the potential risk to human health, they could be banned. This is a misconception. Digestive enhancers are not appetite stimulants and do not make the bird grow any bigger than it otherwise would. It is therefore misleading to refer to them as “growth promoters”.

9. Digestive enhancers reduce the amount of feed nutrients used by the bird to maintain its intestinal flora, freeing more nutrients for absorption, thereby improving the efficiency of feed conversion. They help to prevent diarrhoea and necrotic enteritis which occurs in poultry whether kept for meat or eggs, whether in houses or on free range. The only birds that do not suffer from this condition are those kept in cages because they are separated from their own faeces.

10. The only antibiotics authorised as digestive enhancers are ones that are not used or related to those used in human medicine. Antibacterials which are known or suspected of causing resistance in human bacteria are not used.

11. Clearly any risk to human health should be continually assessed and should take primacy before products are authorised or when authorisations are reviewed. However, in reviewing digestive enhancers the following benefits should be taken into account.

12. Animal Health and Welfare Benefits:

- Control of sub-clinical and clinical diseases such as necrotic enteritis.
- Better utilisation of nutrients.
- Improved bird environment through reduced faecal material, reduced moisture in faeces, and reduced gases all leading to better litter conditions and reduced welfare problems arising from wet litter.
- Improved productivity per se is not a welfare compromise. Confirmation of this has been a legitimate and important part of digestive enhancer approval procedures.

13. Environmental Benefits:

- Less feed required.
- Reduced levels of nitrogen, phosphorus, methane and ammonia entering the environment.
- Lower water consumption.
- Less faecal material produced.
- Fewer vehicle journeys for feed delivery.
- Less arable land required.
- Drier litter facilitating waste litter burning for power generation.

14. Human Health Benefits:

- Provides a drier environment for the birds thus presenting cleaner birds at the slaughter house.
- Probably reduces the overall usage of antibacterials.
- Reduces the use of those antibacterials which are related to those used in human medicine.

15. The Swedish ban on digestive enhancers has only served to confirm the last two points where use of therapeutic antibiotics increased immediately after the ban took effect.

16. It is perhaps worth stating that all these substance are antibacterial in their effect. The modern poultry industry does not use hormonal products of any description to enhance growth or yield.

POTENTIAL ANIMAL SOURCES OF RESISTANT BACTERIA

17. Farm and slaughterhouse staff are exposed to significant levels of bacteria present in live poultry and poultry carcasses. However, an epidemiological study carried out on poultry slaughter plant workers in the USA indicated that even regular close contact did not present a significant risk. Their situation in this respect would be analogous to that of farm and catering staff as well as consumers handling uncooked birds.

18. Catering staff and consumers are exposed to uncooked food which is a potential source of bacterial cross contamination to other food products and utensils, as well as to the food handler unless proper hygiene procedures are observed. Consumption of properly cooked food is not a source of resistant bacteria.

19. Companion animals, particularly dogs and cats which are allowed outside the home environment, are a major potential source of resistant bacteria. Their eating and scavenging habits mean that they are regularly exposed to a range of organisms including *Salmonella* and *Campylobacter*. Contacts between companion animals and members of the household in which they live are such that there is very likely to be a continuous exchange of organisms between them.

20. The level of organisms exchanged would be far greater than that from properly prepared food. It would also involve more members of the household than food preparation. The potential for resistant organisms is likely to be greater in companion animals as they are treated with a far wider range of antibiotics than poultry. There is no requirement for withholding antibiotic treatment before contact. This together with the fact that dogs and cats will have exposure to the excreta of other animals means that if there is any significant transfer of resistant bacteria from animals to man, companion animals are likely to present a much greater risk than food.

POTENTIAL RISK TO HUMAN HEALTH FROM RESISTANT ZOO NOTIC AGENTS OF POULTRY ORIGIN

21. In the case of poultry the two agents that give cause for concern are *Salmonella* and *Campylobacter*. It is indisputable that people can become infected by contact with infected live poultry, carcasses, and improperly prepared contaminated poultry meat. The use of antibiotics in poultry must therefore take account of the potential risk to human health.

22. As both *Salmonella* and *Campylobacter* can survive in the environment and have an extremely wide host range, it is impractical at present to guarantee that poultry will never become infected. This applies even more to poultry on free range than those kept in high quality houses.

23. From an animal health point of view it is not necessary to treat poultry with antibiotics for *Campylobacter* as it does not cause clinical disease in the birds. This is also true in the vast majority of cases of *Salmonella* in poultry. Therefore, if animal health were the only consideration, poultry would very rarely be treated with antibiotics for these two infections.

24. It must be recognised, however, that poultry in which either *Salmonella* or *Campylobacter* is present may be treated with antibiotics for some other bacterial infection. The Industry, therefore, has a responsibility to ensure that such treatment does not add significantly to the number of resistant *Salmonella* or *Campylobacter*.

SALMONELLA

25. CVL has for many years established the antibiotic sensitivity status of all isolates received for serotyping. There is a statutory duty to report all isolates from poultry and submit them for serotyping and this provides an excellent database. It is clear from these figures that, with the exception from time to time of certain phage types of *S. typhimurium*, originating mainly from calves which have a genetic propensity for developing resistance, there has been no significant change in the resistance pattern of salmonella isolates from poultry.

26. The commonest serotype in poultry for the past ten years has been *S. enteritidis* Phage Type 4. This is also one of the few serotypes that, under certain circumstances, can cause clinical disease in poultry. It would therefore, in all probability, have had greater exposure to antibiotics than any other serotype. Nevertheless CVL data indicates that there has been no significant increase in antibiotic resistance (including quinolone resistance) of *S.e.* over the past decade and that the percentage of resistant organisms continues to be minimal.

CAMPYLOBACTER

27. CVL unfortunately does not have a similar database for *Campylobacter*. Dutch and Spanish researchers have however produced some evidence that there has been an increase in resistance to quinolones in campylobacters of poultry origin. This information must be evaluated against their antibiotic usage practices. In Spain there is widespread uncontrolled use of both legal and pirated quinolones. In Holland there was no official authorisation for antibacterials used in animals until recently and a wide range of quinolones, many of which would never receive approval under current legislation, were used during the period covered by the Dutch study.

OPPORTUNISTIC BACTERIA

28. The Industry recognises that normal gut bacteria and opportunistic pathogens such as staphylococci can potentially acquire resistance if birds are treated with antibiotics. Even if they do there is little evidence that these organisms transfer to people. The earlier mentioned epidemiological survey in the USA confirmed that slaughter house workers, in spite of very close contact, did not acquire these organisms, but curiously the same survey demonstrated that vegetarians had a significantly greater percentage of multiple resistant organisms than meat eaters.

TRANSFER OF ANTIBIOTIC RESISTANCE FROM BACTERIA OF POULTRY ORIGIN TO THOSE INCLUDING OTHER SPECIES OF BACTERIA THAT INFECT PEOPLE

29. The Poultry Industry acknowledges that the possibility of this transfer occurring does exist and that it can pose a potential risk to human health. This was recognised in the UK as far back as the 1960s by the Swann Committee. As a result, the authorisation procedures subsequently applied in the UK have taken account of this for all antibacterials, including growth enhancers.

30. The Poultry Industry recognises that scientific advances and the problems arising from the increase in the number of immune-compromised people may require that the use of certain antibacterials in animals be reviewed. The Industry supports such reviews providing they have a sound scientific basis and include a risk benefit analysis.

31. The Industry also accepts that, as long as the foregoing criteria have been fulfilled, any decision must err on the side of caution and that the protection of human health is paramount. The Industry is however concerned that this was not the case with the digestive enhancer Avoparcin. The view of the EC Scientific Committee on Animal Nutrition is well known, as is the work carried out at University of London, Kings College. The former was sceptical of Danish work and the latter cast doubt on the science of the Danish and German research and, therefore, the validity of the conclusions.

32. Perhaps most importantly, Vancomycin resistance in human enterococcae (VRE) is virtually unknown in Denmark where Avoparcin was widely used in pigs and poultry. The converse is true in the US where Avoparcin and related antibacterials have never been used in animals and VRE is a significant problem in human medicine. In spite of this, the authorisation of Avoparcin in the EU was suspended on what appears to be political rather than scientific grounds. The Poultry Industry is concerned at this sort of public circus approach to the licensing of veterinary medicines.

RISK FROM ANTIBIOTIC RESIDUES IN MEAT

33. As the UK poultry meat industry only uses authorised antibacterials and observes statutory withholding periods, all poultry meat reaching the consumer should contain no hazardous antibiotic residues. This safety status of poultry meat has been confirmed by the surveillance carried out by the Veterinary Medicines Directorate and the risk to consumers of acquiring resistant bacteria from the consumption of poultry meat containing antibiotic residues is so small that it can be regarded as negligible.

CONCLUSIONS

34. The British Poultry Meat Industry has a responsibility to meet people's legitimate expectations that poultry meat should be safe and wholesome, and produced from birds kept in conditions of good health and welfare and with the least possible adverse effect on the environment. The responsible use of authorised antibacterials is an essential component in achieving this goal.

35. The Industry continually urges pharmaceutical manufacturers to develop a wider range of vaccines and the Industry promotes research to this end. New vaccines, together with improved housing conditions, are reducing the use of antibacterials.

36. In reviewing the use of antibacterials, their benefits on the health and welfare of the birds, and the human health benefits of retaining poultry meat in the diet should be taken into account. Any significant constraints on availability at affordable prices could have a far greater impact on human health than a relatively small increase in the load of resistant human bacteria which may originate from poultry meat under the proper and controlled use of antibacterials.

37. There is little evidence that the responsible use of authorised antibacterials in meat poultry has led to a significant increase in the load of antibiotic resistant human bacteria in the UK. However antibacterials used in animals must be kept under constant review.

38. The Poultry Industry unequivocally supports the view that human health must take priority in an informed consideration of the use of antibacterials in poultry.

Memorandum by the British Veterinary Association

INTRODUCTION

1. The BVA welcomes to the opportunity of submitting evidence to the House of Lords Select Committee on Science and Technology inquiry into *the rise in resistance to antibiotics and other antimicrobial agents, and its implications for UK and international public policy*.

2. We appreciate that the issues surrounding the use of antibiotics as growth promoters, and for prophylactic and therapeutic purposes in animals and fish are currently under consideration by the Government's Advisory Committee on the Microbiological Safety of Food and that these are not the main focus of the House of Lords inquiry.

3. It is clear, however, that there is increasing concern about a connection (as yet unproven) between the use of antibiotics in animals and human antibiotic resistance. For this reason the BVA is keen to provide the House of Lords Select Committee with information designed to assist and complement the current inquiry. The Association's submission to the Advisory Committee on the Microbiological Safety of Food Working Group on microbial antibiotic resistance in relation to food safety is attached to Annex A.

BVA WORKING PARTY ON THE USE OF ANTIMICROBIALS IN ANIMALS

4. Mindful of the growing fears over alleged antibiotic resistance the BVA has established a working group to examine the use of antimicrobials in animals. There is a need to:

- (a) present an objective view on the use of antimicrobials in livestock and other species;
- (b) reach conclusions based on available scientific evidence; and
- (c) identify studies which might be needed to provide such evidence.

5. The group has not yet completed its task but has done sufficient work to enable it to draw some conclusions and to make a number of recommendations pertinent to the use of antimicrobials in animals. These may assist the House of Lords Select Committee and of course the BVA is very willing to give oral evidence if this were considered appropriate.

6. The group has researched and formed initial conclusions in the following areas:

- (a) the perceived problem: the issue of endangering human health;
- (b) the use of antimicrobials as growth promoters;
- (c) the need for basic research;
- (d) veterinary involvement in practice;
- (e) animal welfare;
- (f) best clinical practice; and
- (g) alternative strategies.

CONCLUSIONS

The Issue of Endangering Human Health

7. The subject of antibiotic resistance has been debated for over 30 years, and there are still no definitive conclusions as to the risk to man from the use of antimicrobials in animals. The consensus view of the available literature suggests that there is an ill-defined risk which may not readily be subject to analysis. A comprehensive form of risk assessment is still awaited.

Use of Antimicrobials as Growth Promoters

8. A wide variety of substances (mostly antibiotics) are authorised for use as growth promoters in the UK, under the EU Directive 70/524/EEC. Licensing requirements, which are rigorous, are at least equivalent to those for prescription antibiotics.

9. The substances—which are usually used at low feed-inclusion levels—have been shown to improve the growth rate and efficiency of feed use in cattle, pigs and poultry. The public health implications of the use of growth promoting antibiotics in animal feed have been examined by numerous official and other bodies on many occasions since 1962. All have discussed the *hazards* but none have proved any *risk* to human health.

10. Should the EU pig and poultry industries lose the right to use properly-licensed antimicrobial growth promoters, there would be very serious implications for the health and welfare of livestock. In addition these industries would be unable to compete in the world livestock markets without subsidies.

The need for basic research

11. A review of published data indicates that there is insufficient information from which to draw sound conclusions on the risks posed to man by antimicrobial use in animals. There is a need to carry out epidemiological studies to aid the generation of a risk assessment of the use of antimicrobials, and the hazards this may pose for human health. Epidemiological surveys have to be a priority for quantifying the problem and defining the risk.

12. It is appropriate that the veterinary profession should make recommendations for research to clarify some of these epidemiological questions. It is important that the answers are applied to other related areas of work such as research into vaccine development, farm and abattoir hygiene, disease eradication programmes and animal traceability—all of which are relevant to the reduction in public health risk from food of animal origin.

Veterinary involvement in practice

13. Food animal veterinarians play a pivotal role in providing assurance on the quality of livestock produce. They are involved:

- (a) *on the farm*, making regular health checks and monitoring animal welfare; monitoring the disease status of the farm and putting in place control measures where necessary; prescribing, controlling and recording the medicines used; passing on information to the abattoir;
- (b) *during transport* in monitoring and enforcement of the health and welfare of animals during transport;
- (c) *in the abattoir* providing the appropriate level of veterinary supervision and food inspection based on the known health status of the animals; passing post mortem/product information back up the food chain to the farm of origin so that problems originating on the farm can be identified and solved.

14. The establishment of a system of data collection and document flow based on a reliable system of traceability is essential to the production of safe food of animal origin. The use of standard protocols for each section of livestock production on a farm should enable both the control of, and a reduction in, risks to animal health, animal welfare, and public health.

Animal Welfare

15. Animal disease is a welfare problem. It is a fundamental concept for both farm and companion animals that they should be maintained in conditions that are as healthy as possible. To sustain optimum conditions of welfare it is imperative for the animal owner and the veterinarian to have access to a range of authorised antimicrobials, which they can utilise to the best advantages of the animal.

16. There are significant differences between the use of antimicrobials in man and animals. In the case of animals, the current product authorisation system allows for the availability of therapeutic prescription only products (POM) and PML feed additive products to be used in a variety of strategies to maintain health and prevent disease. Products will be used in either a prophylactic or therapeutic manner on the basis of the clinical judgement of the veterinary surgeon.

17. Published evidence suggests that the use of PML antibiotics both optimises feed digestion and absorption, as well as providing a local antibacterial activity. Information from Sweden suggests that preventing the use of this type of low-level feed inclusion creates a need for high-level therapeutic antimicrobial use, as well as resulting in welfare problems due to increased disease incidence.

18. When antimicrobial growth promoters are not used in livestock feed there is a reduced efficiency of growth (due to both a loss of feed conversion efficiency and increased levels of disease), and a concomitant reduction in livestock produce output and a fall in farm profits. Additional consequences of a broad economic and social nature have been recorded, ranging from increased feed and water requirements to increased environmental pollution.

Best Clinical Practice

19. The veterinarian must always ensure that animals under his/her care are kept in the very best welfare conditions. Many factors determine the welfare of animals. In the case of food animals, it is essential that both the veterinarian and the livestock owner are fully aware of current legislation. A formal agreement between the veterinary surgeon and the farmer, with carefully specified requirements, could help the food animal veterinarian to ensure that real quality of care is given.

20. The BVA takes very seriously the responsibility on the veterinarian to ensure the safe and proper use of medicines. It is not simply a question of medicines administration but also of testing, sampling and monitoring the effectiveness of medicines. The BVA is revising its document on codes of practice and medicines use. This will be an essential, practical guide to the veterinary surgeon involved in food animal production. It will enable a clear definition of best clinical practice, related also to the use of antimicrobials in any delivery form.

21. The BVA also works to ensure that all members of the profession are informed and motivated in the safe use of medicines. BVA Pharmacy Courses are arranged four times a year and individual species divisions provide other continuing professional development courses.

Alternative Strategies

22. The veterinary profession aims to encourage a greater input into vaccine development, in particular for use with intensive livestock, and also to encourage greater utilisation of disease eradication programmes, farm hygiene systems and study of genetic resistance, as alternatives to the use of antimicrobials.

23. A series of developing technologies may provide alternative or supportive methods of disease control. In particular, the wider application of the competitive exclusion concept, greater exploitation of in-feed

enzymes both to enable utilisation of other feed sources and to provide more effective environmental pollution control. Finally, work in genetic modification and selection for both disease control factors and improved productivity may be the eventual future course of the livestock industry.

24. Antibiotics have been effective in the protection of animal health and welfare over a long period of time. Until equally effective alternatives are available, it would be unwise to remove antibiotics from the veterinary medicines armoury for the treatment of food animals. Any changes to current arrangements should be based solely on scientific evidence.

RECOMMENDATIONS

25. In order to protect public health and animal health and welfare, the BVA considers:

- (a) a key priority should be to conduct epidemiological surveys in order to define and quantify the true situation in terms of antimicrobials use. Further research in this area is vital;
- (b) the veterinary and medical professions should liaise over the perceived problems and co-ordinate research efforts;
- (c) the veterinary profession should explore ways of reducing the use of antimicrobials in disease control. To aid this, studies should be undertaken on the pathogenesis of both zoonotic and non-zoonotic diseases;
- (d) the profession should assist studies into alternatives to antimicrobials, eg the use of vaccines, disease eradication schemes, improved hygiene systems, etc;
- (e) the veterinarians' pivotal role in various links of the food chain should be promoted. The production of safe food of animal origin is dependent upon an integrated approach based on HACCP principles;
- (f) appropriate codes of practice should continue to encourage responsible veterinary prescribing and use of antimicrobials. The BVA will take the lead in informing the profession and providing guidance; and
- (g) changes to current controls or authorisation of approved medicines should be based solely on scientific evidence.

18 December 1997

Memorandum by the Centre for Applied Microbiology and Research (CAMR)

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SUMMARY

The growing problems of drug resistance in micro-organisms are of major public health concern, both nationally and worldwide. Rather than document the evidence for the situation which confronts us, this submission briefly draws attention to some innovative approaches which may contain the seeds of solutions to these problems. These include:

- use of bactericidal phage to control infections;

- SELEX-derived oligonucleotide aptamers as targeting agents;
- antibody-targeted therapeutic constructs;
- novel anti-microbial activities from extremophiles and modified synthetic pathways;
- studies of transfer of drug resistance and treatment of infection;
- defensins and other bactericidal peptides and proteins;
- opsonins and other phagocytic factors;
- bacterial inter-cellular signalling systems;
- mechanisms and genetic control of general drug efflux mechanisms in bacteria; and
- development of vaccines via DNA expression libraries.

In addition, the utility of a specialised unit with particular expertise and equipment for the decontamination of hospital wards and other facilities following outbreaks is outlined.

Recognition of increasingly frequent confrontations with antibiotic-resistant micro-organisms, and concern over the way in which the situation might develop in the future, should lead to action at many levels. Measures to optimise the way in which existing anti-microbial agents are used, and prevent their misuse, will be extremely important in reducing the potential for selection of resistance. However, we believe that the areas of investigation outlined in this document have the potential to broaden the base of possible future responses to the problems presented by drug-resistant micro-organisms, and thus to minimise an undue dependence on existing classes of antibiotics. It is important that exploration of these diverse approaches should be begun soon, in time to provide a spectrum of antimicrobial therapies and vaccines to counter the impressive, and apparently endless, adaptability of the microbial world. CAMR is well-placed to play a pivotal role in the development and assessment of novel strategies such as those outlined here and welcomes constructive discussion and dialogue with interested parties.

1. INTRODUCTION

The introduction of antimicrobial chemotherapy has been one of the most striking success stories of 20th century scientific medicine. It has contributed to remarkable reductions in morbidity and mortality caused by infectious diseases. Despite this evident progress, infectious diseases remain the world's leading cause of death, killing at least 17 million people—most of them young children—each year. About half the human population on earth (approximately 3 billion people) remain at risk of many endemic infectious diseases.

The development of resistance in micro-organisms has been a constant feature of infectious disease medicine, and has followed the introduction of almost every new antimicrobial agent. Until recently this has had only limited consequences, such as occasional complications and deaths or marginally increased healthcare costs, because of the introduction of a constant succession of new anti-microbial compounds. This success encouraged a climate of opinion in developed countries in which such diseases were regarded as mainly of historical interest. However, it is now increasingly recognised that the situation is changing for the worse. Drug-resistant micro-organisms are becoming an increasingly frequent feature in public health, both in the community and in hospitals. There is evidence that important bacterial pathogens are acquiring resistance, some of them becoming virtually untreatable, at a time when few new antibiotics are being introduced or are even under development. This situation is most serious for those diseases for which vaccines are not available and are not likely to be available in the foreseeable future. The maintenance of public health under these changing circumstances requires a flexible and forward-looking strategy by which alternative approaches to treatment or prevention can be developed, assessed and introduced into medical practice.

CAMR is operated by the Microbiological Research Authority in part as a research organisation in the fields of microbiology and biotechnology on behalf of the Department of Health. The prospect of an increasingly difficult climate for antimicrobial therapy represents a serious challenge to CAMR to provide its sponsoring Department with authoritative guidance and productive research. This document is a preliminary survey of possible approaches to the problem which might usefully be adopted. CAMR, by reason of its current portfolio of projects, the experience of its staff with pathogens at various levels of containment, and its laboratory facilities, is well-placed to contribute to them. It is not intended to be an exhaustive list of all possible options for addressing the global problem of anti-microbial resistance, but does explore some avenues which may provide useful and practical approaches.

2. GENERAL CONSIDERATIONS

2.1 Vaccine—or Therapy-based Approaches

There is no *a priori* basis for a general decision on the relative merits of vaccination or therapy. Each problem needs individual consideration as to the optimum strategy, and both approaches are likely to be helpful. The choice will obviously depend on multiple factors such as infection and disease incidence, the

population at risk, and the effectiveness of existing vaccines. In the case of TB for example, an improved vaccine could make a major contribution to disease control, and further research on the design and testing of candidate vaccines would be helpful.

2.2 Impact of Pathogen Whole Genome Sequencing

Increasing numbers of important pathogenic micro-organisms are subjects of complete genome sequencing projects. One of the primary aims of these projects is to identify targets for therapeutic intervention and protective immunogens in unprecedented numbers and detail. During the past two years, six microbial genomes have been completely sequenced, and another 8-10 may be finished before the end of 1997 [1]. These include a number of important human pathogens such as *Haemophilus influenzae*, *Staphylococcus aureus*, *Borrelia burgdorferi*, *Escherichia coli*, *Helicobacter pylori*, *Rickettsia prowasekii* and *Treponema pallidum*. Work is also already under way on the 30-million basepair genome of *Plasmodium falciparum*. It is certain that information flowing from these studies can be and will be applied to the discovery of novel anti-microbial agents and new vaccine candidates. Companies such as Genome Therapeutics and MedImmune have been set up in the US on this basis, and there is also public sector involvement (US Department of Defence Malaria Research Laboratories and NIAID). Human Genome Sciences and MedImmune are collaborating on developing antibacterial vaccines and immunotherapeutics for infections caused by *Staphylococcus aureus* and other pathogens. Much of this sequence information can be accessed over the Internet [2]. Due weight should be given to these considerations in planning any CAMR response in combating drug resistance problems.

3. SURVEY OF NOVEL STRATEGIES

We now outline a number of approaches which we suggest have relevance to a balanced strategic response to problems of microbial drug resistance.

3.1 Use of Bactericidal Phage for Control of Infections

The possible use of bacteriophages for therapeutic purposes has recently been revived [3], and appears to have some merits, particularly perhaps in connection with intestinal tract infections, or with infections of burns or other wounds. Such phages would need to be (a) lytic to destroy their hosts, or alternatively able to deliver some bacteriostatic or bactericidal signal; (b) specific for the pathogen target so as to avoid diversion to irrelevant bacteria and disturbances of the normal gut flora; and (c) non-toxic and non-immunogenic. This last property is likely to be difficult to overcome, although *in vivo* selection of phage mutants may provide a useful approach, and application to intestinal infections or topically to wounds may make this less important. A proof-of-concept test of a prototype version of phage treatment of *E. coli* O157-infected mice could be realised in the short term.

3.2 SELEX-derived Aptamers as Targeting and Coupling Agents

SELEX (Systematic Evolution of Ligands by EXponential enrichment) is a process for recovering ligands with high specificity and affinity from extremely large libraries of oligonucleotides containing tracts of randomly generated sequences[4]. It can be viewed as an alternative to the use of combinatorial libraries of recombinant or monoclonal antibodies, or peptides. Although oligonucleotides generated in this way (aptamers) containing natural bases are susceptible to degradation by nucleases in body fluids such as serum, the use of modified bases can overcome this limitation. The process represents a relatively underexploited method for deriving binding and targeting entities with high affinities for use in novel therapeutic agents. It is important to determine whether aptamers specific for clinically important infectious agents can be obtained, and whether and how these can be applied in alternative treatments.

3.3 Targeted Therapeutic Constructs

The concept of ADEPT (Antibody-Directed Pro-drug Therapy) or targeted drug delivery is capable of extension to delivery of entities active against pathogenic micro-organisms as well as tumour cells, the current focus of such work. Such targeted delivery may allow the use of drugs which under other circumstances have too narrow a therapeutic window for effective application. The targeting moiety could be an antibody as currently used. If so the use of human monoclonal or recombinant antibodies is preferable, to minimise problems of antigenicity or complicated engineering to reduce them. Libraries of human antibody variable regions are now becoming available (eg from the MRC) and provide a source from which such targeting agents can be recovered and developed, subject of course to proper agreements for such exploitation. Further, novel ligands such as SELEX-derived aptamers (see above) may be equally or more effective, and may also be free of complications relating to antigenicity. Various options for the cytotoxic moiety might be considered. Given that the most obvious targets are prokaryotes, the necessity for a pro-drug rather than an active molecule is less necessary. The principal advantage of the targeted delivery is expected to be that lower doses of drug would be effective, and thus unwanted side effects, such as damage to by-stander organisms or

cells would be less likely. This would be particularly important if it enabled the use of drugs presently ruled out because of their unacceptable toxicity, or because of low specific activity. The anti-bacterial peptides discussed in section 3.6 below might have a role. Considerable work on the identification of target molecules, coupling and perhaps release of the active agent and pharmacokinetics would be necessary.

3.4 Novel Antimicrobial Activities

Most currently used antibiotics are natural products (or modifications of them) derived from a fairly restricted class of micro-organisms. More attention to a wider range of organisms could significantly extend the range of potential lead compounds. The unusual physiology and phylogenetic remoteness of extremeophile organisms from current sources of antibiotics increase the possibility that unusual chemical structures will be found. CAMR is already involved in an EU programme aimed towards the screening of marine thermophiles for a range of biological activities, products and enzymes. One of CAMR's roles is to screen organisms and extracts for activities against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis* and *Legionella pneumophila*. Some of these targets were selected because of known associated drug-resistance problems. Preliminary data suggests that an anti-staphylococcal activity may already have been identified. The current programme could readily be broadened to include other potential target organisms.

Another possibility with future potential is to modify the metabolic pathways used by micro-organisms to make currently known antibiotics, so that they produce novel chemical structures which can be screened for antibiotic activity[5].

3.5 Transfer and Emergence of Drug Resistance and Treatment of Infection

The transfer of antibiotic resistance genes from bacteria in normal flora to pathogens in patients, in food animals and foods, and in the wider environment is only partially understood. Gene acquisition by conjugal transfer is well documented, but other mechanisms (such as transformation) were thought to be exceedingly uncommon, as few bacteria are naturally competent in DNA uptake. However, recent evidence suggests that, in natural systems bacteria (including *Escherichia coli*) can quite readily take up exogenous DNA; this has been shown most convincingly in natural waters[6]. Laboratory investigation of these phenomena in conditions modelling natural water systems (with planktonic and biofilm micro-organisms), food surfaces, and the gastro-intestinal tract would allow assessment of the importance of such routes of exchange of genetic information in the spread of antimicrobial resistance.

The emergence of antibiotic resistance could be similarly assessed in experiments using low level or intermittent exposure to antibiotics in *in vitro* model cultures of pathogens, studied in the presence or absence of normal flora, and also in experimental animal models of infection. These experimental models would be suitable for the trial of novel antibiotics and antibacterial therapies, including novel agents (antibiotics, combinations, defensins) and specific bacteriophage. Examples of such studies might include:

- The transfer of antibiotic resistance genes in natural waters, within water system biofilms, or in the presence of the normal skin, pharyngeal of GI tract floras.
- The emergence of drug-resistant *Mycobacterium tuberculosis* in model systems.
- The emergence of resistance in *Salmonella typhimurium* and the use of antibiotics and probiotic approaches to treatment.
- The emergence of vancomycin-resistant strains of *Enterococcus faecium* (VRE) in GI tract flora maintained in model systems.
- Modelling the acquisition of, resistance in, and efficacy of combination treatment of, catheter and cardiac vegetation infections with drug resistant staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA), streptococci and VRE.

3.6 Defensins and Other Antibacterial Peptides and Proteins

There exist a number of classes of peptides which have killing activity against bacteria and other micro-organisms. These include the defensins and β -defensins of macrophages and neutrophils [7,8], similar peptides secreted by mammalian epithelial cells [9], other proline- and arginine-rich peptides in neutrophils [10], and several groups of amphipathic helical peptides from amphibian dermal glands. They fall into four major structural classes— β -sheet structures, α -helices, extended helices and loop structures. All these peptides have membranolytic properties against target cells, and many of the known three-dimensional structures show an amphipathic and strongly cationic character. Their activity does not depend on the presence of specific receptor molecules in the target cell membrane, but is related to pore formation and dissipation of electric potential which lead to cell death [see 11 for review]. Many aspects of their anti-microbial activity are not understood, including details of their mode of action and the target organism specificity displayed by many peptides. Examples of *in vivo* therapeutic activity of these materials are only just beginning to be described [12,13,14], and further work is clearly warranted in realistic models of infection.

These compounds may provide alternative means for treatment of infections refractory to conventional antibiotics, provided further research on their structures, modes of action, immunogenicity, and therapeutic effects *in vitro* and *in vivo* is carried out. The question of specificity of these peptides is particularly intriguing. Some specificity may reside in the lipid composition and structure of the target membrane, and is thus likely to be highly dependent on the growth state of the micro-organisms.

Methods of delivery would also need investigation. There may also be advantages in directing such peptides to bacterial or other targets through coupling to suitable specific ligands; the nature of these and optimum modes of conjugation would also need to be looked at. Delivery of genes encoding antibacterial peptides by bacteriophage might also be a possibility, an interesting synergy with the topic discussed in section 3.1.

One important aspect which it would be essential to explore would be the facility (or otherwise) with which micro-organisms could develop resistance mechanisms to these peptides. If such resistant strains appeared readily, and such resistance was easily transferable, very serious consequences might ensue because of the widespread presence of these protective agents in man, other animals and elsewhere.

3.7 Opsonins and Other Phagocytic Factors

Facilitation of phagocytosis or other killing mechanisms are other possible targets for unconventional intervention in infections. Immune responses involving opsonising antibodies are known to be associated with protection against, for example, *Pseudomonas aeruginosa*. Opsonins facilitate interactions between micro-organisms and phagocytes through the formation of bridging structures, binding a target on the micro-organism at one end and a phagocyte receptor at the other. Examples are the IgG molecule with its antigen-binding and Fc regions, and the C3b complement component, binding to antigen-antibody complexes and to the CR3 receptor on the phagocyte surface. There are also the collectins (SpA, SpD, C-reactive protein, mannose-binding protein), which bind carbohydrates on bacteria and collectin receptors on phagocytes. The questions naturally arise as to whether increased opsonin levels would have positive therapeutic effects, and whether synthetic opsonins—for example bi-specific recombinant antibodies or bi-specific SELEX-derived aptamers (see section 3.2 above), IgG-C3b conjugates or other ligand combinations—could usefully be developed. Indeed, examples of the potential utility of such constructs *in vivo* are already available [15].

There also exist mechanisms of non-opsonic phagocytosis, where receptors on the phagocytosing cell interact directly with pathogen surface features. An example is the macrophage mannose receptor which can bind to capsular polysaccharides on bacterial surfaces. Opportunities for development of compounds to accelerate the process are less obvious, but could centre on methods to upregulate production of such receptors on macrophage cell surfaces.

3.8 Bacterial Intercellular Signalling Systems

It has recently become apparent that many Gram-negative bacteria produce diffusible chemical communication signals (bacterial pheromones) in the form of N-acyl homoserine lactones which regulate diverse physiological processes, including antibiotic production, plasmid conjugal transfer, and synthesis of virulence factors [reviewed in 16]. The paradigm for these diverse activities is the growth density-dependent regulation of the *lux* phenotype in *Photobacterium* (formerly *Vibrio*) *fischeri*, but analogues of the genes involved are widely distributed. Other diffusible small molecule signalling systems, such as the γ -butyrolactones of the streptomycetes, the A and C morphogenesis signals of *Myxococcus* or the oligopeptide mating pheromones of *Enterococcus* are further examples of as yet poorly understood mechanisms which may also be widespread in pathogens. Investigations of the roles and modes of action of these pheromone-like regulatory systems specifically in carefully targeted pathogenic bacteria may provide excellent opportunities for unconventional interventions in disease which would be effective even in bacteria resistant to current antibiotics.

3.9 Mechanism and Genetic Control of General Drug Efflux Mechanisms

It has recently been recognised that bacteria can deploy chromosomally-specified mechanisms of multidrug resistance (Mdr) apparently mediated by efflux pumps [17]. These are additional to and qualitatively different in character from “conventional”, often R-plasmid encoded resistance factors, which often act by enzymatic inactivation of the antibiotic or a class of antibiotics, and which can be acquired from a pool of genes in other microbial genera by a variety of genetic exchange mechanisms. In contrast, Mdrs are intrinsic mechanisms of resistance based on genes which are part of the normal genome of the cells. There is no degradation of the antibiotic, and cross-resistance to many structurally and functionally unrelated drugs occurs. It is possible that these mechanisms have evolved from those required for secretion of factors such as siderophores or excretion of naturally occurring xenobiotics.

Many such systems have been studied in *E. coli* (*acrRAB*, *robA*, *soxRS*, *marRAB*, *emrRAB*), but examples in important pathogens have also been found. The *mexABM* operon, in the laboratory and in clinical isolates of *Pseudomonas aeruginosa*, can mediate resistance to a wide range of antibiotics, including norfloxacin, tetracycline, chloramphenicol, novobiocin, penicillin, cefoperazone, moxalactam and cefpyrone. A similar

system (*mtrRCDE*) has also been found in *Neisseria gonorrhoeae* associated with high levels of resistance to erythromycin, rifampicin, penicillin and crystal violet in clinical isolates.

More work is required to further delineate the importance of Mdrs in clinically important bacterial infections. It is also unknown how the binding of structurally unrelated drugs to components of Mdr systems causes induction or activation of resistance mechanisms involving efflux, and an understanding of how transport of such diverse molecules is performed is also largely missing. Such knowledge might well permit or facilitate design of drugs to avoid or prevent induction or transport, and kill otherwise resistant cells, alone or in concert with conventional antibiotics. It would also help in the implementation of more rational policies on antibiotic usage so as to minimise the emergence of such mechanisms.

3.10 *Development of Vaccines via Expression Library Immunisation*

Increasing prevalence of antibiotic resistance may lead to more emphasis on development of vaccines to a wider range of organisms. We have already referred to the possibilities arising out of whole genome sequencing in section 2.2 above. The new DNA immunisation approach, where plasmid DNA encoding the immunogen rather than the immunogen itself is administered, can be adapted to the discovery of genes encoding protective (or therapeutic) antigens. In this application, already demonstrated successfully for *Mycoplasma pulmonis*, complete genome DNA is fragmented and cloned into a suitable expression vector to form an expression library [18]. Portions of such libraries are used to immunise animals, which are tested for protective immunity. Where such immunity is found, the appropriate library is sub-divided and the process repeated until the protective DNA clone is identified and characterised. Advantages of the method include the possibility of screening hundreds or even thousands of antigens, which would simply not be possible in conventional ways, and the ability to detect protective responses based on cell-mediated immunity. This method might well be applied to important pathogens where antibiotic resistance is increasingly recognised, to rapidly and efficiently discover hitherto unknown antigens for vaccine development. It should also be borne in mind that the application of DNA vaccination might be appropriate beyond the discovery phase, so that protective antigens identified in this manner are actually delivered to vaccinees by intramuscular injection, gene gun or by oral delivery.

4. SERVICE PROVISION

Decontamination of Hospital and Other Facilities after Infection Outbreaks

CAMR has inherited and developed a great deal of experience in the microbiological decontamination of laboratories and production facilities, and in the monitoring and validation of the procedures used. Building on this, an effective system of fumigation for hospital wards which had been contaminated with drug-resistant micro-organisms eg MRSA, could be developed. Current cleaning strategies involve physical wash procedures, and are thus labour-intensive, and of variable efficiency. Fumigation is likely to be very much more efficient and cost-effective, but currently presents problems in wards where forced ventilation to remove the fumigant will provide a hazard to adjacent buildings and personnel. Development of a system for removal of formalin vapour by absorption to a matrix or resin would enable a monitoring and decontamination service for infected wards, operating theatres and buildings to be implemented.

5. RELEVANT EXISTING CAMR ACTIVITIES

The Centre has a great deal of experience in working with micro-organisms at all levels of containment, both in the laboratory and in animal models, and is well equipped to handle potential problems associated with multiple-drug resistant pathogens. A number of existing projects might provide platforms for the development of work specifically targeted at drug resistance.

5.1 *TB, Staphylococci and Streptococci*

Existing DH-funded and other projects on these organisms at CAMR provide a natural jumping-off point for extensions aimed directly at drug resistance problems.

5.2 *ADEPT*

On-going projects in this area involve work on novel microbial enzymes for use in ADEPT and alternative prodrug targeting strategies.

5.3 *Recombinant Antibodies*

Recombinant antibody libraries are a source of one class of candidate ligand for use in targeting strategies; CAMR already has projects investigating and exploiting these agents.

6. CONCLUSION

The Centre is well-placed to play a pivotal role in the development and assessment of novel strategies such as those outlined here and welcomes constructive discussion and dialogue with interested parties. We are ready to build on our current portfolio of projects, the expertise and experience of our staff and our laboratory facilities to make a major contribution to providing solutions to the growing problems of resistance to antimicrobial agents.

Recognition of increasingly frequent confrontations with antibiotic-resistant micro-organisms, and concern over ways in which the situation might develop in the future, should lead to action at many levels. Measures to optimise the way in which existing anti-microbial agents are used, and prevent their misuse, will be extremely important in reducing the potential for selection of resistance. However, we believe that the areas of investigation outlined in section 3 above have the potential to broaden the base of possible future responses to the problems presented by drug-resistant micro-organisms, and thus to minimise an undue dependence on existing classes of antibiotics. It is important that these diverse approaches are explored soon, in time to provide a spectrum of antimicrobial therapies and vaccines to counter the impressive, and apparently endless, adaptability of the microbial world.

REFERENCES

- 1 Fox JL. Microbial genomics: milestones mount exponentially. *Nature Biotech.* 15, 211-212 (1997).
- 2 See <http://www.tigr.org/tdb/mdb/mdb.html>. See also <http://www.hgmp.mrc.ac.uk/Public/genome-db.html> for useful links.
- 3 Merrill CR *et al.* Long-circulating bacteriophage as antibacterial agents. *Proc. Nat. Acad. Sc. USA* 93, 3188-3192 (1996).
- 4 Gold L *et al.* Diversity of oligonucleotide functions. *Ann. Rev. Biochem.* 64: 763-797 (1995).
- 5 Jacobsen JR *et al.* Precursor-directed biosynthesis of erythromycin analogs by an engineered polyketide synthase. *Science* 277, 367-369.
- 6 Baur B *et al.* Genetic transformation in freshwater: *Escherichia coli* is able to develop natural competence. *Appl. Env. Microbiol.* 62, 3673-3678 (1996).
- 7 Paterson-Delafield J *et al.* Microbicidal cationic proteins in rabbit alveolar macrophages: a potential host defense mechanism. *Infect. Immun.* 30, 180-192 (1980).
- 8 Selsted ME *et al.* Purification, primary structures, and antibacterial activities of β -defensins, a new family of antimicrobial peptides from bovine neutrophils. *J. Biol. Chem.* 268, 6641-6648 (1993).
- 9 Eisenhauer PB *et al.* Cryptidin: antimicrobial defensins of the small intestine. *Infect. Immun.* 60, 3556-3565 (1992).
- 10 Agerberth B *et al.* Amino acid sequence of PR-39, isolation from pig intestine of a new member of the family of Pro, Arg-rich antibacterial peptides. *Eur. J. Biochem.* 202, 849-854 (1991).
- 11 Nicolas P and Mor A. Peptides as weapons against microorganisms in the chemical defense systems of vertebrates. *Ann. Rev. Microbiol.* 49, 277-304 (1995).
- 12 Borenstein LA *et al.* Contribution of rabbit leukocyte defensins to the host response in experimental syphilis. *Infect. Immun.* 59, 1368-1377 (1991).
- 13 Hancock REW. Peptide antibiotics. *Lancet* 349, 418-422 (1997).
- 14 Steinberg DA, *et al.* Protegrin-1: a broad-spectrum, rapid microbicidal peptide with *in vivo* activity. *Antimicrob. Agents Chemother.* 41, 1738-1742 (1997).
- 15 Taylor RP and Ferguson PJ. Primate erythrocyte (E) complement receptor (CR1) as an anchor site for bispecific-based therapies to clear pathogens or autoantibodies safely from the circulation. *J. Hematother.* 4, 357-362 (1995).
- 16 Salmond GPC *et al.* The bacterial "enigma": cracking the code of cell-cell communication. *Mol. Microbiol.* 16, 615-624 (1995).
- 17 George AM. Multidrug resistance in enteric and other Gram-negative bacteria. *FEMS Microbiol. Lett.* 139, 1-10 (1996).
- 18 Barry MA, Lai WC and Johnston SA. Protection against mycoplasma infection using expression library immunization. *Nature* 377, 632-635 (1995).

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This response is written from my perspective as Consultant Parasitologist in the United Kingdom National Health Service. In my work at the Hospital for Tropical Diseases (HTD) I am head of the diagnostic parasitology service and organiser of the United Kingdom National External Quality Assessment Scheme for parasitology.

This document deals with parasites of humans only. However, it is worth recording the fact that some important drugs currently used in the treatment of human parasitic infections, notably ivermectin, albendazole and triclabendazole, have come from veterinary parasitology.

1. MALARIA

1.1 Malaria, especially *Plasmodium falciparum*, is the most important parasite of humans. In some parts of the world *Plasmodium falciparum* is resistant to most anti-malarial drugs. For example, in Thailand over the last decade this parasite has become resistant to chloroquine, pyrimethamine/sulphadoxine, quinine used alone (though quinine plus tetracycline is still fairly effective) and mefloquine. In Africa, there is widespread chloroquine resistant *Plasmodium falciparum*. Chloroquine-resistant *Plasmodium vivax* is now recorded in parts of Southeast Asia and the Pacific. Chloroquine resistant *Plasmodium falciparum* first appeared, apparently independently, in Southeast Asia and South America in the 1980s and is now widespread there. If the multi-drug resistant strains of *Plasmodium falciparum* also become established in Africa, the consequences will be much more severe than in South America or Southeast Asia as malaria transmission in sub-Saharan Africa is more intense. Most of the *Plasmodium falciparum* imported into the UK (*Plasmodium falciparum* accounted for 1,283 cases from a total 2,500 malaria episodes reported in the UK in 1996) is from sub-Saharan Africa.

1.2 The pattern of drug resistance apparent from treatment failures in a given geographical area, plus failed chemoprophylaxis in those who have complied with their drug regimens, is taken into consideration when drawing up guidelines for anti-malarial prophylaxis in travellers. For example chloroquine plus proguanil, formerly the recommended regimen for travellers from the UK visiting sub-Saharan Africa has been supplanted by mefloquine as first choice for long-term travellers in the UK guidelines for much of that area. Mefloquine is more expensive than chloroquine plus proguanil and there is a considerable debate at present over mefloquine's side effect profile. The likely pattern for the future is the use of combination prophylaxis and the use of new agents for prophylaxis. This puts up costs and, when a new drug is introduced for use in a very large group of people, may reveal rare but potentially serious side effects inevitably unforeseen by the size of the studies performed for drug registration purposes.

1.3 For treatment, rather than prophylaxis of falciparum malaria, the HTD has ceased to use chloroquine and deploys quinine as first line therapy. So far, significant quinine resistance has been encountered in only a few cases at HTD and these have originated in Southeast Asia.

1.4 Drug resistant malaria should be countered by:

Protection of drugs currently in use, especially mefloquine, atovaquone/proguanil and artemisinin derivatives.

Development of new antimalarials unrelated to quinine to counter resistance.

Development of new radical curative agents active against *P. vivax* and *P. ovale*.

Monitoring of drug sensitivity patterns in malaria parasites imported into the UK.

2. OTHER BLOOD PROTOZOA: TRYPANOSOMIASIS

2.1 This disorder is currently seen very rarely as an imported disease in the UK. The treatment of South American trypanosomiasis (*Trypanosoma cruzi*, Chagas' disease) is very unsatisfactory. The two agents active in acute trypanosomiasis (nifurtimox and benznidazole) are highly toxic. There is no reliable specific treatment for chronic *Trypanosoma cruzi* infection, though this is not the result of acquired resistance on the part of the parasite. There is a need for a non-toxic drug active in central nervous system infection with *Trypanosoma brucei rhodesiense*.

3. SCHISTOSOMIASIS

3.1 An increasing number of patients are being seen at HTD with schistosomiasis, notably *Schistosoma haematobium*. The agent of choice for treatment of schistosomiasis is praziquantel, which acts against *S. mansoni*, *S. haematobium* and *S. japonicum*. There is proven resistance of *S. mansoni* to oxamniquine and suspected resistance of *S. haematobium* to metrifonate. There is now the suggestion of reduced sensitivity of some *S. mansoni* to praziquantel.

4. LEISHMANIASIS

4.1 There has been a recent epidemic of visceral leishmaniasis in the Sudan. Bangladesh also has a large number of cases. This disease is endemic in many Mediterranean countries including Southern France, Spain and Italy. Co-infection with HIV and *Leishmania* is increasingly seen. Resistance to antimonial agents, for example sodium stibogluconate, is established in India and the Sudan. Agents for the treatment of visceral leishmaniasis (sodium stibogluconate, pentamidine and amphotericin B) all have significant side effects, though liposomal amphotericin B is better tolerated than the conventional compound. New, preferably orally active, agents for the treatment of visceral leishmaniasis are needed.

5. INTESTINAL PROTOZOA

5.1 *Cryptosporidium* has been responsible for waterborne outbreaks of diarrhoeal disease in the UK and produces a severe diarrhoeal illness in profoundly immunosuppressed individuals. None of the currently available anti protozoal agents are very effective against *Cryptosporidium*. Paromomycin shows only partial efficacy. Giardiasis can usually be successfully treated with metronidazole or tinidazole, though a few strains are resistant to these agents. Albendazole is an alternative.

The importance of microsporidia as a cause of human disease has yet to be defined. So far, virtually all cases have occurred in immunocompromised individuals. Albendazole is partially effective. Ocular involvement can be treated with topical fumagillin, an agent originally used by beekeepers to treat hives infected with microsporidia.

6. TRICHOMONAS

6.1 Metronidazole resistant strains of *Trichomonas vaginalis* are well documented. As the alternative compounds to metronidazole are also nitroimidazoles, there is a need for new antitrichomonal agents.

7. INTESTINAL NEMATODES

7.1 The existence of *Enterobius vermicularis* (threadworm or pinworm) resistant to benzimidazoles has been suspected in UK practice, but has not yet been proven. There is no UK data on resistance in imported intestinal nematodes such as hookworm, *Ascaris* or *Strongyloides*.

8. GENERAL COMMENTS

8.1 With the exception of malaria and, to some extent leishmaniasis, data on acquired drug resistance in the endoparasites of humans is sparse. The problem needs to be defined by good laboratory and epidemiological surveillance, to determine the presence of clinically important resistance, its geographical location and rate of spread. Only then can strategies for minimising the development and transmission of further resistant strains be developed and deployed.

8.2 Laboratory surveillance for drug resistant parasites will require the development of new assays in some cases.

8.3 In the treatment of many parasites, the drugs are old or have been "borrowed" from our veterinary colleagues. The interaction between veterinary and human parasitologists in drug development should be improved.

8.4 Drug resistant malaria is well established and is a very serious problem indeed. Its study merits high priority.

Dr P L Chiodini

31 December 1997

Memorandum by Professor Ian Chopra, Director Antimicrobial Research Centre, University of Leeds

THE FUTURE OF ANTIBIOTICS: DRUG DESIGN AND MOLECULAR STRATEGY

1. I will address one of the topics raised in the "Call for Evidence", namely the issue of the "Future of Antibiotics: drug design and molecular strategy".

2. Since the 1980s very few new classes of antibacterial drugs have been discovered, reflecting both the challenge of identifying new drug classes and a decreasing commitment to antibacterial drug discovery by the pharmaceutical industry. The same period of reduced introduction of new agents has been accompanied by an alarming increase in bacterial resistance to existing agents and the emergence of a serious threat to global public health. These problems are likely to be further compounded by demographic factors such as global population growth, ageing in developed nations and increased urbanisation which generate optimal

conditions for the transmission of infection. It is therefore possible that we may return to a period, for bacterial infections, that can be likened to the pre-antibiotic era.

3. Since the period between drug discovery and clinical availability can be as long as 10–15 years, increased research activity to discover new agents and therapies is urgently required now before the actual crisis presented by incurable bacterial infections can materialise.

4. This will require active collaboration between researchers in academic and industrial environments in order to optimise opportunities for drug discovery by drawing on the combined expertise and knowledge available in both types of institution. Indeed, the newly created Antimicrobial Research Centre at the University of Leeds specifically seeks to promote academic-industrial collaboration for the discovery of new anti-bacterial agents.

5. In terms of future drug discovery strategies it will be very important to pursue approaches that are likely to minimise, or at least delay, the emergence of bacterial resistance to newly discovered agents when they are eventually introduced into clinical practice. A minimum requirement should be the search for, or design of, structurally novel antibiotics that inhibit new molecular targets. Such agents are unlikely to be susceptible to existing mechanisms of bacterial resistance because of their structural novelty and unique mode of action.

6. The search for new molecular targets to minimise future problems of resistance can be further refined. One approach is not only to seek novel drugs, but also to find new drugs that simultaneously inhibit more than one new molecular target. Simultaneous inhibition of more than one target renders the emergence of resistance less likely since mutations are required in all targets to confer resistance to the drug. Bacterial tRNA synthetases appear to constitute a set of related enzyme targets which may be amenable to this approach. Indeed, some Pharmaceutical drug discovery programmes are already focusing on bacterial tRNA synthetase inhibitors.

7. Another approach that may minimise problems of resistance is to seek inhibitors of bacterial targets that are not only novel in their own right, but are also involved in the disease process itself. The genes encoding such products are intimately involved in the pathogenic process itself and are to be distinguished from the so-called “housekeeping” genes which are required for general growth and survival of the bacterium. New molecular biological approaches are being utilised to discover and characterise bacterial genes involved in infection and it is likely that many of these will only be specifically expressed during infection within the host. For instance, *E. coli* growing in the colon as a harmless commensal organism may express different sets of genes compared to *E. coli* growing in extraintestinal sites associated with septicaemia. The value of developing drugs targeted to infection genes would be selective removal of pathogens at the site of infection only. Since the entire bacterial cell population would not be killed (ie, only those organisms at the sites of infection would be affected), the selective pressure to develop resistance would not be severe.

8. It must be stressed that there are no reports yet even of lead molecules that might comprise drug candidates for inhibition of bacterial pathogenic processes. Public and private resources to fund sustained research programmes in this area will be required to generate proof of concept for a potentially highly valuable approach to the discovery of new anti-bacterial agents.

Professor Ian Chopra

September 1997

Memorandum by Dr D W Denning, University of Manchester

I write with regard to the enquiry into resistance to antibiotics and antimicrobial agents. My submission is exclusively concerned with resistance to antifungal agents in fungi causing life-threatening disease, although in my clinical practice I treat large numbers of patients with many diverse types of antimicrobial resistance including HIV, multiresistant tuberculosis and hospital-acquired infection. My research is however in the antifungal field and I have been instrumental in taking this area forward both nationally and internationally. I have several points to make which I will make succinctly here and most are supported by the accompanying papers.

1. There are only four antifungal agents licensed for use for systemic fungal infections. One of these *flucytosine* is rarely used alone because resistance develops quickly on therapy. *Amphotericin B* was first used in 1957, is only useful if given intravenously and has many toxicities. Recently lipid-encapsulated formulations have reduced toxicity (and increased cost by ~75-fold) but are still only useful intravenously. Little resistance (other than intrinsic resistance) is described against amphotericin B (eg around 1 per cent in *Candida*). *Itraconazole* is only available orally but some resistance is described in *Candida* and our work establishes this year for the first time that resistance also occurs in *Aspergillus*. *Candida* and *Aspergillus* are the leading pathogens causing systemic fungal infections worldwide. *Fluconazole* is not active against *Aspergillus* and resistance is now commonplace in *Candida* against fluconazole.

2. Resistance in fungi may be intrinsic or acquired. Recently there has been a steady increase in the diversity of fungi causing disease in humans many of which are intrinsically resistant to one or more antifungal agents. One example is *Scedosporium prolificans* which is resistant to all known antifungals. We described the first case in the UK but dozens of cases are now recorded in Spain, for example. Clearly new

antifungal agents need to be developed. Several new species of *Candida* including *C. dubliniensis*, *C. inconspicua* and *C. norvegensis* have been described by several groups as causing disease and all are resistant to fluconazole.

3. Acquired resistance is seen particularly in *Candida*. In patients with AIDS fluconazole resistance is seen especially in *Candida albicans* in late stage disease and may be transmitted from one person to another. The mechanisms of resistance appear particularly to be mediated by efflux (eg active transport of fluconazole out of the cell). Acquired resistance is also seen in *Candida glabrata* which is common in leukemia and cancer patients, intensive care and as a cause of vaginal thrush in otherwise healthy women. Resistance may develop in *Cryptococcus* (the most common cause of fungal meningitis worldwide) during long-term suppressive therapy in AIDS.

4. The causes of resistance are not known entirely and much work needs to be done in this area. Exposure to fluconazole is one factor leading to resistance in *C. albicans* in AIDS patients but other factors are probably operative. Emergence of resistant *Candida* in leukaemia and intensive care probably follows increasing use of fluconazole but also may reflect poor handwashing. There is a large study ongoing in the US related to this and we are doing a small (unfunded) study on trying to ascertain where all the resistant *C. glabrata* and *C. tropicalis* infections came from.

5. Resistance to itraconazole in *Aspergillus* is present in about five per cent of isolates we tested from this country. As itraconazole is the only oral drug available for *Aspergillus* infections this is a problem. There appears to be cross-resistance with one of the new azoles in development (SCH) although as this azole is more active this may not matter. There does not appear to be cross resistance to voriconazole but voriconazole is less active than itraconazole or SCH. As infections with *Aspergillus* are acquired from air and it is a ubiquitous organism worldwide, there may be pressures for resistance from azoles used as fungicides in agriculture. One third of the fungicides used in agriculture are azoles. There is no data to support this supposition but some research on this topic is needed.

6. There are several antifungals in development and many companies are working on new ones. Companies active in this area include GlaxoWellcome, Roche, Pfizer, Janssen (Johnson and Johnson), Eli Lilly, Zeneca. Merck, Bristol Myers Squibb, Schering Plough, Takeda (Japan), SS Pharmaceuticals (Japan) Mochida (Japan) and a number of niche/biotech companies. The present worldwide market in agricultural fungicides and for antifungal drugs is about £2 billion worldwide each and the pharmaceutical market is expected to grow to £3 billion by the year 2000. In this way the pharmaceutical industry is playing a significant role in responding to the need in this area.

7. There are only three laboratories in the UK offering a complete antifungal susceptibility testing service. The largest is the Mycology Reference Laboratory in Bristol. This is free to the user because these tests are regarded as specialised (which they are) and reference (which only some are). I run a small laboratory in Hope Hospital which is self-financing by charging and Dr Richardson runs a laboratory in Glasgow which is partially subsidised by Greater Glasgow Health Board and is otherwise self-financing. This patchwork of support impedes the development of services elsewhere and in particular local services and so there is no laboratory in London, for example, doing these tests because it is impossible to compete with a free service in Bristol.

8. There are moves afoot to coordinate the clinical research activities of the European Organisation for Research and Treatment of Cancer's Invasive Fungal Infections Cooperative Group (EORTC IFICG) with that of the US National Institute for Allergy and Infectious Diseases's Mycoses Study Group (NIAID MSG). I have been peripherally involved in discussions which would facilitate international cooperation for clinical studies. This is critically important for the future and the speedy registration of new antifungal drugs. I would encourage the select committee to put its weight behind these proposals (as a model for international cooperation in clinical science) and make recommendations that the MRC and perhaps other funding bodies could facilitate this in addition to the EU.

9. There is a dearth of information about the frequency and nature of fungal infections in the UK and Europe. Very limited data are available on resistance frequency. The committee should recommend the setting up of a national surveillance system, possibly via the PHLS (if they can deliver) for monitoring trends in fungal infections. The British Society of Medical Mycology (BSMM) might be in a position to do this if funded to do so.

10. Laboratory practice in this area is often poor as demonstrated by a survey done recently by the BSMM and the British Society for Antimicrobial Chemotherapy. Accreditation of laboratories needs to have greater emphasis on how specimens for mycology are handled. As a starting point it is agreed internationally that all isolates of *Candida* from "deep" and sterile sites should be identified to species level. This is not happening in many laboratories in the UK. This partly reflects ignorance and partly financial stringency.

11. There are too few clinicians in the UK with a specific interest in fungal infections. This means that it is difficult to effect change in practice at a local level. This partly reflects the insufficient number of infectious disease physicians in the UK as compared with the USA for example but also the opportunities for training. This is a complex area but a general recommendation that there should be more clinicians trained in the management of fungal infections would be a helpful starting point.

Finally, many of these points could be amplified further if you wish either in writing or verbally. The Subcommittee has an important task which I hope will make a real contribution to the management and prevention of infection due to resistant organisms.

David Wemyss Denning

Senior Lecturer and Honorary Consultant in Infectious Diseases, Head, Division of Infectious Diseases, University of Manchester

25 September 1997

Letter from Dr Denning in response to further inquiry specifically about fluconazole resistance in *Candida*

Many thanks for your letter and further enquiry about fluconazole resistance in *Candida*.

The position, six or nine months ago, is as described in our *European Journal of Clinical Microbiology and Infectious Diseases* article, which I previously submitted to the Committee. This can be summarised as follows:

I, and others in Europe, believe that a breakpoint of 12.5 or 16 µg/ml should define resistance because of the lower licensed doses of fluconazole in Europe, compared with USA. Using this breakpoint, the situation can be summarised as:

1. *Candida albicans* causing candidaemia—3 per cent resistance in the UK (Hope Hospital) compared to 7 per cent in Spain, 13 per cent in the USA. There is no reason to suppose that the figure is any lower or higher for any of the other syndromes caused by *Candida albicans*, such as oral or vaginal thrush. However, surveys have not been systematically done in the normal population.

2. *Candida albicans* in AIDS—Resistance is frequent in patients with AIDS, particularly late stage AIDS with the figures varying from around 10–33 per cent of isolates being resistant to fluconazole. This is heavily influenced by prior fluconazole exposure.

3. *Candida krusei*—all such isolates are resistant to fluconazole but the frequency of infection with *Candida krusei* (which is almost always systemic) varies substantially from hospital to hospital.

4. *Candida glabrata*—the majority of isolates are intermediate or resistant to fluconazole and, if they are not at the beginning of therapy, they may develop resistance on therapy. *Candida glabrata* is an increasingly common cause of candidaemia in intensive care patients, etc, and causes 5–10 per cent of cases of vaginal thrush.

5. *Candida tropicalis*—resistance is relatively common. The graph which I submitted with my previous papers shows the rising incidence in resistance in *C. tropicalis*, in our experience (rising to 80 per cent). *C. tropicalis* is an invasive pathogen and only rarely causes other syndromes.

6. *Candida parapsilosis*—This organism is almost never resistant to fluconazole in vitro and is commonly associated with the use of plastic intravascular devices and prosthetic heart valves. Patients may fail therapy with fluconazole, despite in vitro susceptibility, primarily because their intravascular devices are not removed and changed.

7. Other species of *Candida*—resistance is occasional, although rather unusual species recently identified, such as *C. dubliniensis*, *C. norvegensis*, *C. inconspicua*, are frequently fluconazole resistant.

You asked specifically about the potential role over-the-counter fluconazole might have had in the induction of resistance. There is no data on this and to my knowledge it is not being studied, in the UK at least, but there are several situations in which it could possibly be of importance. These are:

1. In increasing the proportion of cases of vaginal thrush that are due to *C. glabrata*, which is typically fluconazole resistant (though not so often itraconazole resistant).

2. Altering the gut yeast flora to include a larger proportion of fluconazole resistant isolates in women who subsequently have major surgery, significant trauma, or who require transplantation or cytotoxic chemotherapy for leukaemia would increase the likelihood of infection and fluconazole-resistant yeast species. Clearly study of this in a systematic way is difficult.

In summary, fluconazole resistance is common. Much of the advertising that Pfizer have distributed is based on data generated prior to registration (eg the late 1980s) when fluconazole resistance could not be tested. This gives an inappropriately reassuring message to the medical profession. There is clearly a need to monitor resistance to fluconazole and other antifungals after their introduction. Something could be built into the obligations of the pharmaceutical company on licensing a new antifungal. As you may know, we have at least five new azole compounds in clinical development at present.

I hope the above is helpful. Please come back to me if you require any more thoughts or facts.

David W Denning, MB BS, FRCP, MRCPATH, DCH

Senior Lecturer/Honorary Consultant, Infectious Diseases.

27 October 1997

Memorandum by Glaxo Wellcome

Glaxo Wellcome recognised the increasing problem of antimicrobial resistance some time ago. In 1994 we launched a major collaborative research programme, "*Action tb*," which is aimed at the discovery of new medicines for the treatment of tuberculosis and novel approaches to vaccination for the prevention and control of the disease. In 1995 we established, in partnership with the Department of Health, the Medical Research Council and the Biotechnology and Biological Sciences Research Council, the Edward Jenner Institute for Vaccines Research. The objective of this Institute is to carry out basic research to underpin our understanding of the immune response to important pathogens and malignant cells in order to discover new approaches to vaccination.

THE GLAXO WELLCOME CONTRIBUTION TO ANTI-INFECTIVES RESEARCH

Glaxo Wellcome has significant programmes of antimicrobial research, both inside the Company's own laboratories and also with external academic groups, aimed at discovering new medicines for the treatment of bacterial infections or prevention of infectious diseases.

At the beginning of last year GW made anti-infective research one of its priority areas for drug discovery. We have strengthened the Company's own research resources devoted to this field by approximately 50 per cent and in particular we are investing significantly in bacterial genomics and genetics. The majority of our research scientists and technologists who are engaged in the study of antimicrobial resistance and the search for new anti-infective medicines are based at our research laboratories in Verona, Italy. These are supported by other scientists based at our Medicines Research Centre at Stevenage.

Our "*Action tb*" programme involves collaborations between Glaxo Wellcome's scientists and external research groups in the School of Hygiene and Tropical Medicine and St Mary's Hospital School of Medicine in the University of London, the Department of Infectious Diseases in the University of Birmingham and several research groups in the Republic of South Africa. This five year programme is funded by Glaxo Wellcome to the extent of £2 million per year.

We are a major contributor to the recently established Edward Jenner Institute for Vaccine Research which is incorporated as a Company limited by Guarantee and is a Registered Charity. This Institute is now established at Compton, Berkshire, and will by the end of 1997 have a scientific and technical staff of over 30 carrying out basic research into the nature of the immune response against pathogens and at understanding the relationships between host and pathogen. In addition to its research role the Institute also has a role in training young research scientists in the vaccine field and in increasing public awareness of the value of immunisation. Glaxo Wellcome is providing £10 million to build and equip the new Institute and is also committed to contributing 50 per cent of its running costs over the next 10 years. Our contribution will amount to £3 million per year from 1998 onwards.

OUR APPROACH TO ANTI-INFECTIVES RESEARCH

We firmly believe that the opportunities offered by genome sequencing, for the identification of novel antibacterial targets, will fundamentally swing the pendulum back in favour of the pharmaceutical industry in our fight against infectious diseases. Revolutionary new developments in microbial genetics allow us to construct whole biosynthetic pathways in antibiotic producing microorganisms and from the new insights deriving from such studies we are able, for example, to tailor novel macrolide structures. To help us in this we have recently entered into a major collaborative research agreement with scientists in the University of Cambridge in the field of combinatorial polyketide biosynthesis. We are hopeful that this strategy will allow us to design new antibiotics not susceptible to present macrolide resistance mechanisms. Looking at the process of antibacterial research as a logical flow, we are able, using bioinformatics tools to quiz bacterial genome sequence databases, to identify common targets present in a range of bacterial pathogens. Manipulation of bacterial genes, through gene knockouts for example, can then be used to validate the essential nature of these targets. At the same time such knowledge allows the cloning and expression of target proteins for the design of high throughput screens. These screens are then used to detect chemicals which will interfere in some way with the action of the target protein in a way that may provide useful anti-infective activity. We are also, in some instances, able to construct "smart cell" assays to detect antibiotic activity in which hypersensitive bacterial mutants are used which will respond to inhibitors more readily than a "normal" organism.

We are also pursuing a radically different approach, a so-called "disease-based" approach, as part of our antibacterial strategy. This involves us in identifying all of the genes required by a particular pathogen in order to cause disease. The products of these genes can then be used to provide targets for novel agents which the potential to prevent the bacterium from causing infection. It has been argued that it will be more difficult for an organism to develop resistance to drugs which work in this way without losing its inherent ability to cause disease. Thus the organism will be rendered incapable of causing disease.

Isolated protein target or "smart cell" screens can be used to look for novel chemical leads, and we routinely now look to a variety of sources, including compound libraries kept in-house, natural products, such as plants, fungi and bacteria, and combinatorial chemistry libraries. We are now able to achieve throughput

rates in excess of 50,000 compounds per week by using robotic technology and this rate of testing means that we can now aim to progress about 10 new targets into high throughput screening every year. This increases our overall chances of success in discovering novel anti-infective compounds.

A number of target molecules identified in pathogenic organisms through the study of bacterial genetics are also being crystallised and their molecular structures determined. Information derived from such studies, and also from studies of co-crystallised bacterial proteins with their bound inhibitors, is now providing us with insights into the mechanisms of antibiotic resistance developed in bacteria. They also allow us to model the active sites of target molecules and to design novel chemical structures capable of interfering with the active site and of overcoming or preventing the development of effective resistance by organisms. Such inhibitors, it is hoped, will lead to new anti-infective agents active against resistant infectious agents. Using this approach we have studied the binding of the staphylococcal gyrase enzyme with novel inhibitor molecules. We have used these techniques to gain a clearer picture of the molecular basis of resistance to sulphonamides by studying the mutations occurring in the sulphonamide binding site of the target enzyme dihydropteroate. The knowledge we now have of the active site of this enzyme is providing us with insights which could lead to new classes of antibiotics effective against sulphonamide resistant organisms.

NON-ANTIBIOTIC APPROACHES TO INFECTIOUS DISEASES

We believe that the ultimate means of controlling infectious diseases in communities is through the use of vaccines against the invading organisms. However, the state of knowledge of the immune response against many pathogens, and also the nature of the host/parasite interaction in determining the pathogenesis of the disease, is not yet adequate to allow the design of effective novel vaccines against many of the important pathogenic organisms. This is the reason why our Company went into partnership with the Department of Health, the MRC and BBSRC to create the Edward Jenner Institute which is now undertaking basic strategic research in this field. Such research is essential if we are to expand the knowledge base necessary for progress in this field. There is also a need to discover better adjuvants for use with vaccines. This is a field that has remained dormant for many years with little progress being made. As our knowledge increases of the cellular and molecular biology of immune responses, particularly in respect of the mechanisms of antigen presentation, novel means enhancing adjuvant activity should become possible. There are also other developments in the vaccine field, such as the use of DNA from pathogenic organisms, which we believe may provide some real advances towards effective control of pathogens.

Other approaches to the control of treatment of infectious disease could be through the use of novel agents capable of modifying the immune response or the mechanisms of pathogenicity. These approaches are also under active consideration by Glaxo Wellcome.

PROGRESS TOWARDS NEW ANTI-INFECTIVE AGENTS

We have had considerable success in the past in our search for novel antibiotics. For example Glaxo Wellcome has discovered an entirely synthetic class of β -lactams in the trinem series of antibacterials which was specifically designed to overcome the resistance to penicillins and cephalosporins mediated by changes to the target enzymes involved in cell wall biosynthesis that is increasingly common in pneumococci and staphylococci. One such compound, sanfetrinem, has recently completed Phase II clinical studies.

Using the new approaches to screening to discover new anti-infective agents, described above, we already have five series of novel compounds with interesting and novel antibacterial activity, including compounds active against antibiotic resistant Gram-positive pathogens and *M. tuberculosis*. A substantial proportion of our activity is now aimed at optimising these exciting leads and converting them into new antibacterial drugs.

We have also been successful, using essentially the same process of high throughput screening and lead optimisation, to identify a novel antifungal drug which overcomes the increasing problem of azole-resistance in AIDS-related fungal infections.

OPTIMISING THE USE OF EXISTING ANTI-INFECTIVE MEDICINES

The increasing problem of the development of resistance by bacteria to commonly used antibiotics will be discussed in more detail below. We believe that the presently available antibiotics could be used more effectively to limit the further development of resistant organisms. For example, in those areas in which there are high levels of penicillin/ampicillin resistant *S. pneumoniae*, *M. catarrhali*, *H influenzae* these agents should not be used because their performance is compromised and their use drives further resistance by selective pressure.

In the future new antibiotics, directed against the organisms via a number of different mechanisms, should be used in combinations or on a cyclical basis which may prove to be a more effective means of controlling infections and limiting the development of resistance. Physicians should be encouraged to utilise a wide range of new antibacterial agents thereby sweeping away the agents to which resistance has developed and also lowering the selective pressure on any one mechanism of action. In addition to the problems of bacterial and

fungal resistance, Glaxo Wellcome has an excellent record of promoting the rational use of combination anti-retroviral therapy to prevent or reduce the emergence of resistance in AIDS patients on long term, maintenance therapy. We have also successfully developed a combination antimalarial product, Malarone, which is active against chloroquine-resistant *Plasmodium* and are distributing this through a donation programme in parts of east Africa.

WHAT FORCES ARE AT PLAY IN THE GENERATION OF ANTIMICROBIAL RESISTANCE?

The widespread use of antibiotics in animal husbandry has also been cited as one of the possible culprits. Others have suggested that failure of patients to complete their course of treatment can lead to emergence of resistance. It can also be argued that irresponsible prescribing of antibiotics for human use is an important contributory factor in the development of antibacterial resistance. Thus inappropriate prescribing of antibiotics for viral or self-limiting conditions or the continuing use of obsolete medicines with poor antibacterial activity and poor pharmacokinetic or pharmacodynamic profiles which result in sub-optimal doses will tend to increase selective pressures. Our view is that the appropriate use of antibacterials is to use them less, but also to use the better agents that have different mechanisms of actions than the drugs to which resistance has been developed, or which have improved resistance profiles.

The recent lessons learnt from anti-retroviral chemotherapy has demonstrated the very powerful effects that natural selection can have, even when prescribing is entirely appropriate and patients are highly motivated to comply with treatment. It would be our contention that selection of resistant organisms is an inevitable consequence of antibiotic usage, but that more rational prescribing is an important mechanism for reducing the rate at which resistance emerges.

In order to make prescribing more rational, and in the absence of rapid points of care diagnostics, a knowledge of resistance patterns is one mechanism to achieve this. Glaxo Wellcome co-operates with local health authorities to provide information to guide prescribing in community and hospital-based practices. We are also in contact with the WHO surveillance programme with the objective of both contributing to, and reacting to, knowledge of resistance emergence and spread. To gain clinical benefit from this information, flexible prescribing guidelines can be a useful aid both in the community and hospital setting. The emphasis must be on flexibility, to enable nimble, local responses to changes in resistance patterns.

IMPEDIMENTS TO PROGRESS IN OVERCOMING THE RESISTANCE PROBLEM

Approximately five years ago, critical voices were still being raised against pharmaceutical research aimed at so-called "me-too" antibiotics. This caused industry to question its commitment to the area, with the result that many companies reduced their efforts in antibacterial drug discovery. Added to this discouragement is the natural conservatism of physicians to use new agents, this is particularly true in the UK, which drives a type of "moral hazard". Thus unless there is a true need for new medicines then they will not be developed; but, because there is a need to be met, the present trend is for new agents to be "reserved" to particular circumstances, as a last resort possibly, rather than be used more widely. This trend is increasingly being driven by economic considerations rather than clinical ones. This situation leads to the industry questioning its investment, or potential investment, in this therapeutic area as they will not get the return on investment they require and which would be possible with a wider use of new agents. The outcome will be a "deprioritisation" of this area in favour of others.

Recognition by Government agencies and other healthcare providers that antibiotics provide great benefits in reducing morbidity and mortality and, in doing so, reduce other forms of health care expenditure, eg nursing and ICU costs, and decrease time off work with its consequent loss production, is needed to reverse this trend. A new paradigm must be developed by the industry and the healthcare providers. This was alluded to by Sir Richard Sykes, Chairman of Glaxo Wellcome, at a recent meeting of globally recognised infectious disease specialists when he said "if you have the vision, we'll deliver the products". The expansion of our knowledge, particularly of the bacterial genome, will allow a flow of new products to combat infectious diseases which should mean that there should no longer be a need to "reserve" new anti-infective medicines. Antibiotics represent great value for money!

Finally the decline in microbiology, and particularly bacteriology, in UK universities is having an adverse effect upon the ability of companies to conduct anti-infectives research in this country. In particular it is becoming increasingly difficult to recruit graduates of the quality and with the skills we require. As mentioned above, Glaxo Wellcome now carries out a very significant amount of its anti-bacterial research in Italy. It is we believe important that the universities are encouraged, and enabled, to provide training to provide the skilled microbiologists need by our industry and others to carry out research in this field which is at the cutting edge of the subject and of international standard.

Memorandum by Professor David Greenwood, University Hospital, Queen's Medical Centre, Nottingham**SUMMARY**

Problems of antimicrobial drug resistance are presently serious, but not yet desperate. The principle areas of concern are twofold: multiresistant opportunist bacteria that affect vulnerable patients in high dependency areas of hospitals (the most pressing problem for developed countries); and multidrug resistance among classis pathogens like *Mycobacterium tuberculosis*, *Salmonella typhi*, *Shigella* spp., *Neisseria gonorrhoeae* and *Plasmodium falciparum* (mainly, though not exclusively, a problem for developing countries). The first type can be contained to a large extent by good infection control practices and careful prescribing based on agreed policies of antimicrobial drug use; the input of infection control nurses and laboratory-based clinical microbiologists is crucial and these services deserve full support. The second type additionally requires co-ordinated action to regulate more effectively the manufacture, distribution, promotion and use of antimicrobial drugs; in this case the input of governments, international agencies and pharmaceutical houses is essential. Prescription-only status for antimicrobial drugs used in man and animals should be the norm. The number of drugs available for the treatment of viral, fungal and parasitic infections is comparatively small and much less is known about resistance. More research in these areas would be welcome. Teaching good prescribing habits to medical students is presently haphazard and needs to be formalised. Surveillance needs to be improved. The second half of the 20th century has been a golden age of antibiotics, but the outlook is uncertain. If antimicrobial chemotherapy is to have a secure future, prescribers must learn to use these powerful tools with greater discretion and their use worldwide must be effectively regulated.

1. THE PROBLEM OF RESISTANCE

Microbes are remarkably adaptable and amazingly versatile. Through the course of evolution they have developed sophisticated mechanisms for preserving genetic information and disseminating it efficiently in the interests of survival. They recognise no boundaries. Resistance developing in one part of the country, or, indeed, of the world can be disseminated readily. Similarly, non-human use of antimicrobial agents is a potential source of resistance in man; for example, resistant micro-organisms developing as a result of the use of antibiotics in animal husbandry may reach man through direct contact with those animals or through the food chain.

Bacteria

Because we have so many antibacterial agents (at least 200 different drugs are on the world market for the systemic treatment of infection¹, of which about 85 are available in the UK²) the treatment of bacterial infection in the community at large is relatively secure. However, the apparent richness of available resources must be judged alongside the ability of micro-organisms to acquire the capacity for multidrug resistance: certain mechanisms of resistance can negate the therapeutic efficacy of a whole family of antimicrobial agents (eg methicillin-resistant *Staphylococcus aureus* (MRSA) are resistant to all penicillins, cephalosporins and related β -lactam antibiotics); and the genetic information for unrelated resistance mechanisms, affecting numerous agents, can be assembled on transmissible genetic elements. Especially problems may arise with infections caused by micro-organisms for which therapeutic options are, for particular reasons, already narrow. Tuberculosis and typhoid fever are good examples.

Of course, in many countries of the world therapeutic choice is already severely restricted for economic reasons. It is partly because of the restricted availability of affordable antimicrobial drugs (but also because poverty provides the conditions in which infectious diseases flourish) that many of the most acute problems of resistance are borne by communities in the poorer nations.

For countries with advanced health care systems the major area of concern is the treatment of vulnerable patients in high dependency areas of hospitals³. Here, patients become colonised or infected with opportunist microbes, some of which are already intrinsically resistant to many antibacterial agents, or have developed multiple-resistance through the selective pressure of intensive drug use. Often, these problem organisms are indigenous to particular units, though the opportunity for spread may (and does) occur as patients are transferred to other wards or between institutions. Such multiply-resistant opportunist pathogens are not usually a threat to the general community, since they are mostly of low intrinsic virulence. However, multiresistant *Staphylococcus aureus* may represent an exception, since staphylococcal infection is fairly common in domiciliary practice and some of these infections require antimicrobial therapy.

Viruses, fungi and parasites

In contrast to the profusion of agents available for the treatment of bacterial infection, the number of chemotherapeutic drugs for diseases caused by viruses, fungi, protozoa and helminths is relatively small. Moreover, such agents as are available often belong to closely related groups of compounds, so that the possibility of cross-resistance may exacerbate the potential problem of drug resistance (eg most antifungal agents are either azole derivatives or polyenes). Resistance to antimalarial drugs in *Plasmodium falciparum*,

the species of malaria parasite that is estimated to be responsible for 1.5 to 2.7 million deaths each year, is causing particularly severe problems⁴.

A fair amount of research is presently directed towards understanding aspects of resistance to antifungal and antiviral agents, but more needs to be done. Mechanisms of resistance to chemotherapeutic agents directed against protozoa⁵ and helminths⁶, and the epidemiology of such resistance, are poorly characterised. The only real exception is malaria where a considerable amount of work has been carried out. The lack of interest in antiparasitic agents is largely due to the fact that much protozoal infection and most helminthic infection in man is borne by the poorer countries of the "Third World". However, concerns about parasitic infection also impinge on the developed world: millions of people travel each year to areas in which malaria is endemic; some cosmopolitan protozoal diseases, like, cryptosporidiosis, are presently untreatable; others, like trichomoniasis, are virtually untreatable in the event (at present fortunately rare) of nitroimidazole resistance.

Despite the fact that more than 1.25 billion people harbour intestinal worms, and many millions suffer from the effects of systemic worm infections, most research on drug resistance (and drug development) in helminths has centred on parasites of animals^{6, 7}. Yet therapeutic choice in serious conditions such as schistosomiasis and filariasis are severely restricted; in the case of hydatid disease (which occurs in the UK) they are virtually non-existent.

2. FREQUENCY OF RESISTANCE

We still do not understand the factors that govern how resistance develops, even in bacteria, which have been extensively studied. Twenty-five years after the introduction of penicillin into widespread use, 90 per cent of strains of *Staph. aureus* encountered in hospitals were resistant to the drug, but this is not the norm. In the same period all other organisms within the spectrum of penicillin retained full susceptibility, and many have remained sensitive to this day. Among organisms responsible for infections for which antibiotics are commonly prescribed in domiciliary practice (eg, urinary tract infection), the level of resistance to the drugs used generally seems to stabilise at between 20 and 40 per cent. Different selective processes are at work with different drugs and micro-organisms. So-called "infectious drug resistance" disseminated by well characterised genetic transfer mechanisms is important in many cases; in others a slow, step-wise process (eg penicillin resistance in pneumococci), or both (eg penicillin resistance on gonococci) may operate.

A great deal of work has been done in this area^{8, 9}, particularly in its molecular epidemiological aspects, but many practical questions remain unanswered, in particular, the conditions of drug use that favour the emergence of resistance are poorly understood. Similarly, more needs to be learnt about the effects of reduced selective pressure on the prevalence of resistance. Reductions in drug usage have been found to be associated with a decline in the prevalence of resistance in some cases¹⁰, but there is also evidence, at least *in vitro*, that resistance may not always confer a disadvantage when selection pressure is removed¹¹.

3. EDUCATION

Control of antimicrobial drug resistance presupposes careful, informed prescribing. Use of antimicrobial agents appears deceptively simple, but rational prescribing requires a good deal of thought and knowledge. Quite apart from the vast number of different agents (often with confusingly similar names) with which the prescriber has to cope, he or she needs to be familiar with the pharmacological properties of the drugs, the formulations available, potential side effects, special needs for children, the elderly and other groups, and the benefits and limitations of antimicrobial intervention in individual infective conditions¹².

In addition, there are a number of problems peculiar to these drugs. Prescribing antimicrobial agents differs from the use of other formulary compounds in two ways: 1. Unlike drugs that are designed to influence a physiological system in the patient, antimicrobial agents are intended to target selectively a living micro-organism, which is inhabiting a variably-accessible location within the host and which has triggered a complex immunological response. Antimicrobial therapy should ideally be selective in the sense not only of avoiding unwanted side effects, but also in supporting the immune response and leaving the normal microbial flora intact. 2. Use of antimicrobial agents, unlike other treatments, always has implications beyond the welfare of the patient receiving the drugs, since it adds to the pressure for the development of resistance. Although failure of therapy owing to the development of resistance in the infecting organism during treatment is unusual, except with certain drugs for which the selection of pre-existent resistant mutants may occur, resistance among other organisms of the patient's normal flora may be promoted and alter the balance within the general bacterial ecology.

At present, teaching on antimicrobial chemotherapy in the UK (and elsewhere) is spasmodic¹³. Nottingham may be unique in offering a two-week module on antimicrobial therapy for third year medical students about to start their clinical training. Generally, knowledge of antimicrobial agents is gleaned from a few lectures within the general microbiology or pharmacology teaching, while it is intended that practical prescribing should be learnt at the bedside. Equally little is done at the postgraduate level, while the pharmaceutical industry are very active in promoting their products. Publications like *Drug and Therapeutics Bulletin* and *Prescribers' Journal* help, but are inadequate of themselves.

A thorough knowledge of the properties of antimicrobial drugs and an understanding of what they will, and will not do, is essential in the control of antimicrobial drug resistance. The use of antibiotics for conditions in which bacteria are unlikely to be involved (such as viral respiratory infection) or in which antimicrobial drug therapy offers only limited benefit (eg, most diarrhoeal illness; acute recurrences of herpes simplex) should be discouraged during the prescribers' formative training. The subject of antimicrobial chemotherapy needs to be given a much higher profile in the medical curriculum and at the postgraduate level.

4. ROLE OF INFECTION CONTROL AND CLINICAL MICROBIOLOGY SERVICES

Hospitals in the UK are fortunate in that they usually have excellent on-site laboratory facilities, with well-trained technical staff and medically-qualified consultants, who act at the interface between the laboratory and the wards to give expert advice on the diagnosis and management of infection. Most large centres also have clinical infectious disease specialists. The supportive reference and epidemiological monitoring functions of the Public Health Laboratory Service (with its network of peripheral laboratories that carry out the diagnostic service work in many hospitals) are also first-rate. In addition, this country has pioneered the development of control of infection teams (often led by a consultant microbiologist) who formulate and monitor policies of hospital infection control, co-ordinate the response to problems of infection and perform an important educational role. It is hard to quantify the benefits that accrue from these activities since they are largely indefinable (infection prevented, unnecessary use of drugs pre-empted, expensive ward closures avoided etc), and the educational role is often carried out through informal conversation. However, in the context of antimicrobial drug resistance, it is hard to escape the conclusion that the generally successful containment of major resistance problems in the UK owes a great deal to these activities.

In recent years an increasing squeeze on resources has put a great deal of strain on these services and morale has suffered. Well-equipped and well-staffed laboratories, with good clinical liaison are essential to the fight against antimicrobial drug resistance (reference 14; copy enclosed). Adequate support needs to be provided for clinical microbiology laboratories, infectious disease units and control of infection teams.

5. SURVEILLANCE

National surveillance

The surveillance of antimicrobial drug resistance in the UK (and elsewhere) is presently unco-ordinated, although the PHLS and the British Society for Antimicrobial Chemotherapy have recently initiated a collaborative venture to formulate standard procedures that should lead to better information in the future. There are several pitfalls that must be avoided if useful information is to be obtained: surveillance must be tailored to different circumstances so as to answer specific questions, thus, surveillance of the prevalence of resistance among organisms causing urinary tract infection in the community obviously requires a different approach than that needed to monitor the development and spread of resistance within an institution, where the problems may be inherent to that institution, or even be unit-based within it. Another problem is that of obtaining reliable denominator data. For example, simply examining organisms routinely isolated from specimens submitted to the laboratory is liable to introduce bias because of the likelihood that resistant organisms from patients who have failed empirical therapy will be over-represented.

International surveillance

Although carefully targeted local and national surveillance is most important in defining and addressing many problems of antimicrobial drug resistance, there is also a need to monitor developments internationally. The World Health Organisation is attempting to co-ordinate such information through its Antimicrobial Resistance Monitoring Programme¹⁵ (with the associated WHO Network scheme¹⁶). This is an important step forward and deserves full support.

6. REGULATION

Availability of antimicrobial drugs

Procedures for the licensing of drugs and the control of advertising in the UK are generally good. One area of concern, however, is the question of over-the-counter availability of drugs. Whatever the pros and cons of wider availability for other prescription drugs, the trend towards relaxing prescription-only status for antimicrobial agents^{17,18} must be resisted. Self-medication is likely to lead to suboptimal use of these agents with a concomitantly greater risk of the development of resistance¹⁹. It is a matter of considerable anxiety that two of the agents presently available over the counter, aciclovir and fluconazole, represent important therapeutic drugs that belong to groups of antimicrobial agents (antiviral and antifungal agents, respectively) that are far from plentiful. The development of widespread resistance to these agents would have serious consequences.

Genetically-modified products

The use of antibiotic resistance genes as selective markers in genetically-modified products is not likely to pose a threat to the use of antibiotics in man, since mobilisation of these genetic elements seems unlikely to occur and the resistance markers used are, in any case, already common in environmental bacteria. Nevertheless, the use of these markers is unnecessary and, for this reason, it would seem prudent to avoid such use.

Non-human use of antimicrobial agents

The overall contribution to resistance of the use of antimicrobial agents in agriculture is a matter of dispute, though it seems clear that antibiotic-resistant enteric bacteria, including salmonellae, are reaching man from animal sources. This issue has been examined before in the Netherthorpe Report (1962)²⁰ and the Swann Report (1969)²¹ but the time is probably ripe to revisit the matter. The question of whether use of antibiotics as growth promoters is still effective in the light of modern methods of animal husbandry needs to be examined. Little is known about the impact, if any, of other non-human uses of antimicrobial agents.

Regulation as a global problem

Regulation of the manufacture, distribution, advertising and use of drugs, including antimicrobial drugs, in many countries outside the UK, notably nations of the developing world, is an area of great concern. Poor quality products, inadequate storage, improper usage (often encouraged by unscrupulous advertising of inappropriate formulations and drug combinations), open availability, inadequate dosage and illicit marketing abound²²⁻²⁵. Government, international agencies and voluntary organisations do what they can, but more co-ordinated action is necessary²⁶ and more pressure needs to be put on the pharmaceutical companies to regulate their own activities in areas of the world in which abuses are common.

7. PROSPECTS FOR NEW ANTIMICROBIAL AGENTS

Antibacterial agents

In the half-century from 1945 to 1995 a steady flow of new antibacterial agents became available. Most of the major antibacterial drug families had been discovered by 1960. Since then efforts have focused on developing derivatives of these compounds with improved properties, especially compounds specifically aimed at overcoming resistance mechanisms that were making the older drugs unreliable. For the rich resources now available we are indebted to the pharmaceutical industry, notably in Europe (including the UK), Japan and the USA, which carried out nearly all of the research and development needed to maintain the flow of new compounds. It is unlikely that this situation will continue for several reasons: the cost of research and development is extremely expensive; the market for antibacterial agents is crowded; the returns are uncertain; and a number of compounds that have been marketed have not proved sufficiently profitable. It has been claimed that the process of drug development from discovery to marketing takes about 12 years and costs *ca* \$359 million; only one in 6,000 starter compounds reaches the market, and only 30 per cent of products that do survive actually yield a profit²⁷. Nonetheless, there is still some interest in antibacterial agents within the pharmaceutical industry and new techniques of molecular modelling, combinatorial chemistry etc are expected to yield compounds that might be progressed if a market need is identified²⁸.

Agents active against other types of infection

In contrast to antibacterial compounds, the search for antiviral and, to a lesser extent, antifungal agents is still being energetically pursued. The potential market, especially for effective, non-toxic drugs for viral diseases, is huge. All the major pharmaceutical companies are actively looking at these areas. The possibility of stimulating, or otherwise modifying the host response to infection by modulating natural biological mechanisms is also being actively investigated, but has so far met with only modest success. Research into antiparasitic agents is largely confined to those of potential use in animal husbandry. Occasionally, this yields compounds that prove to be of value in human medicine.

Vaccines

Vaccination has been spectacularly successful in the control of many infectious diseases. In the case of smallpox total eradication has been achieved. Prospects that poliomyelitis may also be eradicated are good, and the WHO's Expanded Programme on Immunization has been very successful. Much good work continues in this area, boosted by the recent success of *Haemophilus influenzae* conjugate vaccines. However, vaccines are unlikely to be the answer for the generality of infective conditions. In parasitic diseases, notably malaria, efforts to produce an effective vaccine have been continually frustrated. Moreover, vaccines have their own problems, not least those of cost and the logistics of distribution. The risk of side-effects, however

rare, is a barrier to acceptance by the general public and a disincentive to manufacturers because of the possibility of costly litigation.

The ability of the drug houses to come up with ever more potent antibacterial agents has, until now, blunted the impact of bacterial resistance. The necessity to husband the rich resources available for treatment of infection by careful and circumscribed use has not been seen as a high priority. Such wastefulness can no longer be afforded.

REFERENCES

- 1 O'Grady F, Lambert HP, Finch RG, Greenwood D (eds) *Antibiotic and Chemotherapy* 7th edn. Churchill Livingstone, 1997.
- 2 *British National Formulary* Number 33 (March 1997).
- 3 Goldman DA *et al.* Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *Journal of the American Medical Association* 1996; 275: 234-240.
- 4 World Health Organization. World malaria situation in 1994 Part 1. *Weekly Epidemiological Record* 1997; 72: 269-274.
- 5 Borst P, Ouellette M. New mechanisms of drug resistance in parasitic protozoa. *Annual Review of Microbiology* 1995; 49: 427-460.
- 6 Taylor MA. Anthelmintic resistance in helminth parasites of domestic animals. *Agricultural Zoology Reviews* 1992; 5: 1-49.
- 7 Roos MH. The molecular nature of benzimidazole resistance in helminths. *Parasitology Today* 1990; 6: 125-127.
- 8 Chadwick DJ, Goode J (eds). *Antibiotic resistance: origins, evolution, selection and spread* (Ciba Foundation Symposium 207), John Wiley & Sons, 1997.
- 9 Amyes, SGB, Gemmell CG (eds) Antibiotic resistance. *Journal of Medical Microbiology* 1997; 46: 436-470.
- 10 Swartz MN. Use of antimicrobial agents and drug resistance. *New England Journal of Medicine* 1997; 337: 491-492.
- 11 Schrag SG, Perrot V. Reducing antibiotic resistance. *Nature* 1996; 381: 120-121.
- 12 Greenwood D (ed.) *Antimicrobial Chemotherapy* 3rd edn. Oxford University Press, 1995.
- 13 Davey P *et al.*, A survey of undergraduate and continuing medical education about antimicrobial chemotherapy in the United Kingdom. *British Journal of Clinical Pharmacology* 1993; 36: 511-519.
- 14 Greenwood D. What's the use of susceptibility testing? *Chemotherapy* 1997; 9 (Suppl. 1): 7-12.
- 15 WHO Antimicrobial Resistance Monitoring Programme website: <http://www.ch/programmes/emc/amr/amrfacts.htm>.
- 16 Anonymous. The WHO network on antimicrobial resistance monitoring. *Weekly Epidemiological Record* 1996; 71: 185-187.
- 17 Anonymous. Over-the-counter drugs. *Lancet* 1994; 343: 1374-1375.
- 18 Pringle M. Access to Antibiotics: a case for change in category. *Journal of Antimicrobial Chemotherapy* 1995; 36: 577-579.
- 19 Reeves DS, Lewis DA. Over the Counter anti-infectives—of benefit to whom? *Journal of Antimicrobial Chemotherapy* 1995; 36: 579-584.
- 20 Agricultural Research Council and Medical Research Council. Report of the Joint Committee on antibiotics in animal feeding. HMSO, London, 1962.
- 21 Report. Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine (Swann Report). HMSO, London, 1969.
- 22 Melrose D. *Bitter pills: medicines and the Third World poor*, Oxfam, 1982.
- 23 Chetley A. *A healthy business? World health and the pharmaceutical industry*, Zed Books, 1990.
- 24 Chetley A, *Problem Drugs*, Zed Books, 1995.
- 25 Editorial. Quality control and essential drugs. *Lancet* 1997; 350: 601.
- 26 Kunin CM. Resistance to antimicrobial drugs—a worldwide calamity. *Annals of Internal Medicine* 1993; 118: 556-561.

- 27 Billstein SA. How the pharmaceutical industry brings an antibiotic drug to market in the United States. *Antimicrobial Agents and Chemotherapy* 1994; 38: 2679-2682.
- 28 Chopra I. Approaches to antibacterial drug discovery. *Expert Opinion on Investigational Drugs* 1997; 6: 1019-1024.

**Memorandum by Professor Brian Henderson and Professor Michael Wilson, Eastman Dental Institute,
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NOVEL APPROACHES TO THE DEVELOPMENT OF ANTIBACTERIAL AGENTS

INTRODUCTION

1. The development of antibiotics in the 1950s generated a hubristic state of mind for which we are now paying the price. The belief that mankind had conquered infectious disease took hold of the popular imagination as well as those who should have known better. For example, the Surgeon General, in his address to the United States Congress in 1969 stated "We can close the book on infectious diseases". While there was some evidence to bolster this view, it was apparent from the very beginning of the antibiotic age that bacteria could develop resistance both to natural and synthetic antibiotics. Antibiotics are the secondary metabolites of bacteria or fungi, evolved to kill or inhibit the growth of competing species. It is this evolutionary history of antibiotics which encompasses the ultimate futility of developing new antibiotics. Bacteria have evolved strategies which are likely to eventually overcome the actions of any antibiotic. However, there are other strategies which can be developed to combat infections. It is the purpose of this short document to bring some of these (ie those which our group have invented, have developed or have an interest in) to the committee's attention.

NOVEL ANTI-BACTERIAL STRATEGIES

2. Five strategies will be briefly outlined:
 1. Killing bacteria by altering their local environment.
 2. The use of light-activated antimicrobial agents.
 3. Development of antimicrobial peptides.
 4. Use of commensal bacterial/host interaction mechanisms for therapeutic development.
 5. Cytokine blockade.

ENVIRONMENT-MODIFYING AGENTS

3. The Cellular Microbiology Group at the Eastman Dental Institute, University College London has pioneered an ecologically-based approach to killing anaerobic bacteria associated with the most prevalent chronic infectious diseases of man—the periodontal diseases. This involves the topical application of redox-poisoning agents to alter the environment within the disease lesion so preventing further growth of the causative organisms. It would be virtually impossible for anaerobic bacteria to develop resistance to such agents as this would have to involve a wholesale change in their physiology.

LIGHT-ACTIVATED ANTIMICROBIAL AGENTS

4. Another approach developed by the Cellular Microbiology Group is the use of low-power laser light to generate bactericidal molecules (singlet oxygen and free radicals) from photoactivatable drugs. The singlet oxygen and free radicals then kill neighbouring bacteria by damaging their cell walls and membranes. This has proved to be capable of rapidly killing a range of micro-organisms including epidemic strains of methicillin-resistant *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Helicobacter pylori* and *Candida albicans*. Clinical evaluation in primates looks encouraging. Clinical application of this technique (known as Photodynamic Therapy) would be of greatest value for the treatment of skin, wound and burn infections as well as infections of the oral cavity. The major advantages of the approach are: (i) an almost instantaneous microbicidal effect (ie within seconds or minutes) unlike antibiotics which have to be administered for days or even weeks (ii) killing is localised so that there are no disturbances of the normal microflora at other sites (iii) development of resistance to singlet oxygen and free radicals would be extremely unlikely.

DEVELOPMENT OF ANTIMICROBIAL PEPTIDES

5. While the majority of antibiotics are non-peptidic secondary metabolites, bacteria make a number of peptide-based antibiotics. It now turns out that every living organism on this planet makes specialised antibacterial molecules which have been termed antibiotic peptides. However, this nomenclature is incorrect as the word "antibiotic", in its strictest sense, refers to compounds made by microorganisms and a better

terminology would be antimicrobial peptide. These molecules are short peptides (12–40 odd amino acids in length) which appear to have a generic mechanism, killing bacteria by forming pores on their surface. This causes the bacterium to leak intracellular fluid and die. Experimental studies have shown that preventing insects producing such antimicrobial peptides results in their death from the overgrowth of their own normal microflora (see next section). The apparent advantage of these antimicrobial peptides over conventional antibiotics is the minimal degree of resistance that bacteria seem to have developed to them. This may reflect their mechanism of action at the bacterial cell wall. A small number of companies are exploring the potential of antimicrobial peptides by trying to create active non-peptidic versions of the natural molecules. This is an area ripe for development.

THERAPEUTIC POTENTIAL OF COMMENSAL BACTERIA/HOST CELL INTERACTIONS

6. Our instinctive fear of infectious bacteria is mitigated by the knowledge that while the average human is composed of 10^{13} cells it contains 10^{14} bacteria. In other words 90 per cent of the cells in the human body are bacteria. We are prone to infection by only a few dozen bacterial species yet those bacteria which populate our bodies are extremely diverse and more than 1,000 species may live on and within us. These include organisms such as *Staphylococcus aureus*, *Neisseria meningitidis* and *Haemophilus influenzae* which can cause devastating and lethal diseases.

7. The ability of the human body to support this astronomical number of bacteria, which are variously termed the normal microflora or the commensal microflora, creates a paradox. All the bacteria constituting this normal microflora (such as the three bacteria mentioned) can cause severe inflammation. However, the fact that we survive most of our lives without succumbing to our own normal microflora shows that these bacteria do not cause inflammation. This raises a question which our Cellular Microbiology Group has only recently begun to answer—what prevents the bacteria constituting the normal microflora from inducing inflammation? We propose that the major reason that we do not become inflamed in response to our own normal microflora is that they produce proteins which damp down any inflammation which they may produce. We have called these proteins bacteriokines and believe that by understanding their mechanism of production and action we could explain how it is that we fail to respond to our own normal microflora. More importantly, these bacteriokines could be of therapeutic importance in the treatment of bacterial infections and could provide a novel method of dealing with the sequelae of bacterial infections.

CYTOKINE BLOCKADE

8. The symptoms of bacterial infections are largely due to the actions of a large group of newly-discovered proteins which are produced by all animals. These proteins, which are known as cytokines, have hormone-like actions and act to integrate local cell behaviour. They play key roles in homeostasis and are the main integrating signals in innate and acquired immunity. Unfortunately, overproduction of these cytokines, such as occurs in infections, can produce severe pathology and even death. The classic examples of this are the shock conditions induced by Gram-negative (septic shock) and Gram-positive (toxic shock) bacteria. It is estimated that in the USA these two conditions kill around 200,000 people each year. There has been enormous interest in blocking the actions of certain cytokines as a treatment for human diseases. Currently, clinical trials are underway in London and other centres of a neutralising antibody to the pro-inflammatory cytokine-tumour necrosis factor (TNF) α for the treatment of the chronic inflammatory disease, rheumatoid arthritis. Preliminary results look very promising.

9. In infections, the production of cytokines is protective but often the production becomes uncontrolled and serious symptoms develop. We need to be able to control the production of cytokines such that physicians can control the side-effects of their production, while leaving the protective actions intact. It is likely that by understanding how bacteria control the induction of cytokines that such therapeutic control can be exerted.

CONCLUSIONS

10. We would suggest that effective future therapies for infectious diseases can only be developed if we fully understand the interactions which occur between bacteria and human cells in both the normal organism and during specific infections. Such understanding should provide therapeutic targets and the means to tackle them. The development of effective therapeutics for many of mankind's idiopathic diseases requires pharmaceutical companies and academics teaming up and this is leading to the development of many novel drugs.

**Memorandum by Dr R L R Hill, MEd, PhD, MIBiol, CBiol,
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1. SUMMARY OF RECOMMENDATIONS

Establish Nationwide Mandatory reporting of drug-resistant pathogens.

Improve the status of research on antimicrobial agents, resistance and infection control within medical schools and other institutes of health research, through stated recognition by the UK Government and the European Administration.

Make the comprehensive teaching of medical microbiology, including antimicrobial chemotherapy and infection control, a mandatory and examinable part of undergraduate medical curricula.

Promote judicious use of antimicrobial agents by continuing medical education in medical microbiology.

Establish a surveillance system, jointly between Public Health Laboratories and Teaching Hospitals, to monitor and periodically publish resistance trends.

Establish the requirement for Health Authorities to take account of trends in resistance and produce treatment guidelines.

Establish a system within the Medical Control Agency, so that the licence and use of antimicrobial agents in animal husbandry may be properly considered in the context of antimicrobial resistance and medical treatment, rather than a component in the microbiological safety of foods.

Promote European legislation with respect to the use of antimicrobial agents and reporting of drug-resistant pathogens.

Promote research on new drugs and vaccines.

Promote research on risk factors, outcomes of infection and the microbiology of resistant organisms.

2. INTRODUCTION

There is a growing recognition that a vast proportion of morbidity and mortality that is not traumatic or environmental, is either genetic or infective. During the last 20 years, an intriguing constellation of new infectious entities, including bacteria such as *Campylobacter species* (food poisoning and gastro-intestinal infection), *Escherichia coli* 0157:H7 (food poisoning), *Helicobacter pylori* (peptic ulceration and gastric cancer), *Clostridium difficile* (pseudomembranous colitis), the protozoan *Pneumocystis carinii* (pneumonia in the immunocompromised), Hepatitis viruses C to G (blood-born hepatitis and liver cancer), Human Immunotropic Virus (AIDS) and the prion *nv*-CJD (new spongiform encephalopathy variant of Creutzfeldt Jacob Disease), have been identified or recognised. Whilst antiviral agents are still in their infancy, the discovery, development and clinical use of antimicrobial agents during the 20th century have substantially decreased the morbidity and mortality caused by infection with pathogenic bacteria. Although the development of antimicrobial agents for the chemotherapy of bacterial infections represents one of the most remarkable achievements of this century, this is effectively being laid to waste by the increasing emergence of bacterial pathogens that have acquired resistance of these agents. This seriously threatens the effectiveness and antimicrobial chemotherapy for the treatment of both hospital- and community-acquired infections, and has serious implications for medical microbiology, public health and medical education. The escalating problem of antimicrobial resistance has been muted to herald the dawn of the "post-antibiotic era".

3. THE PROBLEM

Antimicrobial treatments have, until recently, been successful for treating infection caused by newly recognised bacterial pathogens as well as existing and often classic bacterial infections, such as those caused by *Staphylococcus aureus*. However, widespread use of antimicrobial agents both in humans and in animals, has put selective pressure on bacteria such that resistance has evolved to produce multiply-resistant pathogens. Infections caused by these drug-resistant bacteria are difficult, and more recently, impossible to treat.

4. SOME ESSENTIAL TERMINOLOGY AND CONCEPTS

4.1 *Antibiotics*: these are natural substances produced by various micro-organisms to aid their survival in ecosystems. Many antibiotics are now partially or totally synthesised and some anti-infective chemotherapeutic agents are purely synthetic substances. The term "*antimicrobial agents*" describes all anti-infective drugs. *Multiple-resistance* refers to micro-organisms resistant to two or more clinically usable antimicrobial agents.

4.2 *Bacterial strains*: like all forms of life, bacteria are subject to genetic variability within a species, which produces different strains, in much the same way that humans vary one to another and between populations. The differentiation between strains is important for infectious control and epidemiology and the laboratory methods by which this is achieved are referred to as *typing*.

4.3 *Cross-infection* occurs when two or more patients are infected or colonised with the same strain of a given bacterial species. In cross-infection, the transmission of bacteria is commonly mediated by the hands of ward staff.

4.4 Many bacteria that cause infection are carried by healthy individuals. *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* are major pathogens carried in the nasopharynx by a small percentage of the population. *Staphylococcus aureus* is also carried in the nasopharynx as well as the axillae and perineum by up to 40 per cent of the population, depending on epidemiological circumstances. In carriage, organisms are consistently isolated from a specific anatomical site. Colonisation is the process by which bacteria attach to human cells, eg of the skin or mucosa, and is a prerequisite for carriage. When bacteria that cause cross-infection are highly prevalent, such as in a hospital outbreak, the epidemiological pressure produces an artificially high colonisation and carriage rate. In such circumstances, patients and staff may become temporarily colonised and serve as reservoirs for infection. Nurseries, Nursing homes, Hospitals and close communities such as colleges and military barracks, are all areas where the epidemiological pressure favours transmission of pathogens.

4.5 The *Gram-stain* is a laboratory method fundamental to the identification of bacteria. Most bacteria are divided into Gram-positive or Gram-negative rods or cocci. Gram-positive bacteria have a different spectrum of sensitivity to antimicrobial agents than Gram-negative bacteria. Human skin and the oral cavity is predominantly colonised by Gram-positive bacteria, whilst the gut is predominantly colonised by Gram-negatives.

5. A BRIEF HISTORY OF ANTIMICROBIAL CHEMOTHERAPY AND BACTERIAL RESISTANCE

5.1 Bacteria have been the major cause of death in human populations, until the antibiotic era began in the 1930s. It is now well-recognised that the world is facing a global threat from the resurgence of infectious diseases and the emergence of new pathogens. International travel, the free movement of people and the world-wide distribution of foodstuffs are already exposing populations to pathogens on a scale previously unprecedented.

5.2 The sulphonamides were the first antimicrobial agents to be introduced into clinical practice in the 1930s, followed by penicillin in the 1940s and a plethora of other classes of antimicrobial agents, including many derivatives of penicillin, tetracyclines, macrolides, cephalosporins, carbapenems, aminoglycosides, glycopeptides and the quinolones that collectively, have been highly effective in treating bacterial disease. However, some seventy years after Fleming's discovery of penicillin, some pathogenic bacteria are resistant to nearly all clinically usable antimicrobial agents. At the very least, this poses problems for surgery, as modern operations are often complicated and involve compromised hosts, and would not be possible without the prophylactic administration of antimicrobial agents to prevent infection.

5.3 There is a continuing problem with bacteria that have stable resistance characteristics and pathogens giving rise to immediate concern are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VREF) and *Klebsiella pneumoniae*. *S. aureus* were originally sensitive to penicillin but this species is now considered penicillin-resistant for purposes of antimicrobial treatment. This resistance was acquired during the early fifties due to the increased incidence of naturally resistant strains that produced a beta-lactamase, an enzyme that destroys penicillin, and the wide dissemination of the transmissible genetic determinants for this enzyme. In the late fifties, tetracycline resistance was acquired and a strain referred to as the "golden staph", because of its slight yellowish pigmentation, spread world-wide, causing serious infection. Enterococci, including *E. faecium*, are common commensals of the gut but can cause infections associated with prosthetic devices, particularly in compromised patients such as those receiving liver transplants. The acquisition of a transferable genetic element that confers resistance to vancomycin and all available glycopeptides used in human and veterinary medicine and animal husbandry, by *E. faecium*, has caused infections impossible to treat without recourse to "synercid", an experimental agent. Fortunately, *E. faecium* are not aggressive pathogens but there is great concern that *S. aureus* and other more pathogenic Gram-positive bacteria, could acquire resistance to vancomycin, the mainstay for treating infections caused by multiply-resistant Gram-positive bacteria. Multiple-resistance is usually associated with the ability to spread.

5.4 In 1959, multiply-resistant strains of *Shigella dysenteriae*, which cause dysentery, were isolated in Japan and in the late 1960s and early 1970s, multiple-drug resistance began to take hold by emerging first in *S. aureus*, and subsequently in a variety of Gram-negative rods such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, which are common pathogens in hospitalised patients. Multiply-resistant strains of *Salmonella* have now found their way into the food chain and in Africa, many strains of *S. dysenteriae* are resistant to all usable antibiotics except the fluoroquinolones. There are further concerns about the slow increase (resistance is higher outside the UK) of resistance to penicillin in pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria gonorrhoeae* and *N. meningitidis*, that cause infection in the community.

5.5 Genetic determinants for beta-lactamases have become widely disseminated and have been acquired by many bacterial species and continually undergo genetic mutation to produce modified enzymes that destroy the large variety of penicillins and related drugs available today. *Klebsiella* are naturally more

resistant to penicillin but have been continually evolving enzymes such as beta-lactamases, to cope with new drugs. The latest drug active against multiply-resistant Gram-negative rods such as *Klebsiella*, is meropenem. At King's we have had problems with a strain of *K. pneumoniae* that is multiply-resistant and meropenem-resistant. Infections with totally resistant bacteria are not treatable with antimicrobial agents.

5.6 The incidence of tuberculosis (TB) is now on the increase in Europe and the USA, added to which the recent problem of multiply-resistant *Mycobacterium tuberculosis*, the cause of TB. *M. tuberculosis* infects one-third of the world's population and already causes some three million deaths each year. The recent resurgence of TB in the USA was accompanied by resistance to the two most effective drugs, isoniazid and rifampicin, and such strains are being isolated in the UK. *M. tuberculosis* has increasing opportunities to cause infection due to the number of individuals infected with HIV. The greater the number of individuals infected with *M. tuberculosis*, the greater the opportunity for further dissemination to close contacts who would not otherwise become infected.

5.7 Resistance is sometimes due to a variety of strains of any given species of bacteria or, alternatively, may be due to the predominance of one or a small number of successful strains. To be able to differentiate between strains of pathogenic bacteria and to identify genetic markers for epidemicity or infection, is essential for infection control and treatment of patients, as well as improving our understanding of the medical microbiology and Public Health aspects of bacterial pathogens.

5.8 *S. aureus*, with particular respect to MRSA

5.8.1 My particular expertise concerns MRSA. The following (paras 5.8.2 to 5.8.5) briefly describe the practical problems associated with this multiply-resistant pathogen. (Please also see the following useful publications: Casewell & Hill, 1986; Hill & Casewell, 1991; Hill & Casewell, 1992; and Tabaqchali, 1997).

5.8.2 *S. aureus* is the second commonest cause of wound infection in hospitalised patients and a major cause of septicaemia. In general, these organisms are a common cause of skin and wound infection, bone and joint infection, endocarditis, food poisoning and meningitis following trauma. *S. aureus* also causes toxic shock syndrome associated with cotton tampons. For skin and wound infections, General Practitioners will prescribe Flucloxacillin, which is almost specifically an antistaphylococcal drug that is not destroyed by the beta-lactamase enzymes that most infecting strains of *S. aureus* produce (*S. aureus* is, for practical purposes, regarded as resistant to penicillin). Flucloxacillin is derived from "methicillin". Resistance to methicillin confers resistance to all penicillin-derived drugs, including cephalosporins. Since the emergence of multiply-resistant MRSA in the 1980s, vancomycin, a glycopeptide antibiotic, has been the drug of choice for the treatment of serious infection caused by these organisms. Because many strains of *S. aureus*, such as epidemic MRSA (EMRSA), are readily transmissible between patients via the hands of ward staff, *S. aureus* often causes outbreaks of infection that require patients to be isolated. Isolation facilities are not always available and patients cross-infected with epidemic strains, and in particular EMRSA, have to be barrier nursed on the ward.

5.8.3 In the case of EMRSA, patients and staff have to be screened for carriage of the organism. Patients colonised or carrying EMRSA also have to be isolated and receive appropriate treatment to eliminate the organism to prevent further cross-infection. In the recent past, carriage of MRSA during hospital outbreaks has been controlled by the use of mupirocin, a topical antibiotic. Staff who are nasal carriers receive intranasal treatment with mupirocin and, because of the effectiveness of mupirocin, have only had to stay off duty for two days. These aspects of infection control are now complicated by mupirocin-resistance and it is proving difficult to prevent these EMRSA from circulating between Hospitals and nursing homes. And this means that these resistant organisms become more prevalent and increasingly difficult to control.

5.8.4 Resistance to mupirocin has probably emerged faster because of inappropriate use where, for example, patients have been applying ointment containing this antibiotic to their skin for over a year. Research carried out in the Department of Medical Microbiology at King's has shown that up to 3 per cent of coagulase-negative staphylococci (ie, species other than *S. aureus*) isolated from urine or blood before the introduction of mupirocin, were naturally mupirocin-resistant and that in some strains, this resistance was transferable to *S. aureus*. Resistance to mupirocin has now appeared in EMRSA, and in particular, EMRSA type 16, which has affected over 400 patients at King's since 1992. Whilst mupirocin-resistant EMRSA constitute only a proportion of circulating strains of EMRSA, the isolation of these organisms threatens infection control as, at the moment, no other agent has been proved to reliably eliminate these organisms.

5.8.5 For systemic treatment, the only reliable drugs to treat infection with these pathogens have been glycopeptides, vancomycin and the relative newcomer, teicoplanin. If MRSA are not controlled, then the clinical use of vancomycin or teicoplanin rises because of the increased number of wound and blood stream infections in hospitalised patients. The ultimate emergence of vancomycin-resistant MRSA has been anticipated since it was shown experimentally that genes from vancomycin-resistant enterococci may be transferred into *S. aureus*. At about the same time isolates of *S. aureus* with decreased sensitivity to vancomycin and teicoplanin were also found. This year, the isolation of glycopeptide-resistant MRSA in Japan and other parts of the world has been reported. At King's we have isolate low-level glycopeptide-resistant EMRSA from diabetic foot ulcers. These patients have been on long-term treatment with

teicoplanin, which has saved many of these patients from having amputations. We now have to monitor these patients carefully, withdraw teicoplanin when signs of increased resistance emerge and look for alternative treatments, which is not an easy task.

6. CRITICAL FACTORS IN THE EMERGENCE OF RESISTANCE

6.1 *Genetic basis for the inevitable development of resistant bacteria*

6.1.1 Bacteria have one chromosome, compared to 22 in human cells. However, unlike human cells, bacteria have additional circular pieces of DNA referred to as plasmids. These are readily exchanged between bacteria. In addition, there are short pieces of DNA that can move from chromosome to plasmid, or from either the chromosome or plasmids of one bacterium to another.

6.1.2 Because antibiotics are natural substances, many bacteria in nature have genes that enable them to resist the antibiotic substances produced by other micro-organisms. Both plasmids and transposons contain resistance genes, and as they move from bacterium to bacterium, they may acquire small changes to their DNA (by mutation or recombination) which can enhance the survival of bacteria during antimicrobial treatment. The ability of bacteria to acquire and accumulate resistance genes from other members of the normal bacterial flora under the selective pressure of antimicrobial use, is the basis for the development of multiple-drug resistance. It has been shown, for example, that the van A vancomycin-resistance gene cluster in *Enterococcus faecalis* can be transferred to *S. aureus*. Although an isolate of *S. aureus* with high-level resistance to vancomycin has yet to be encountered, low-level glycopeptide resistant (vancomycin and teicoplanin) *S. aureus*, including MRSA, are now beginning to be isolated. This development has serious public health implications. We have also found at King's that mupirocin-resistant strains of coagulase-negative staphylococci, which are part of the normal flora, existed before the introduction of mupirocin. Resistance genes have probably circulated from these few naturally resistant strains into the pathogenic *S. aureus*, showing the importance of normal flora in the circulation of resistance genes.

6.2 *Selective pressure as the driving force*

6.2.1 Selective pressure is exerted on bacteria by the widespread use of antimicrobial agents and is therefore the driving force in the development of bacterial resistance. Prescription of a systemic antibiotic to treat any given infection also exerts selective pressure on other bacteria that colonise the gastrointestinal tract, upper respiratory tract and the skin. The incidence and prevalence of drug-resistant bacteria is associated with the prescription mass of antimicrobial agents directly or indirectly linked to the observed resistance. In Spain, a close correlation has been shown between the annual consumption of penicillin and the incidence of penicillin-resistance in *S. pneumoniae* from 1979 to 1989. The increasing use of beta-lactams (penicillin and derivatives), particularly with those cephalosporins, monobactams and carbapenems that have poor activity against enterococci, have played a role in the development of beta-lactam-resistance in *Enterococcus faecium*. Resistance rates of *S. pneumoniae* to macrolides such as erythromycin, is higher in France than other European countries, which correlates with the higher prescription mass for these antimicrobial agents in France compared to elsewhere.

6.2.2 In the UK, the Public Health Laboratory Service found recently that there is about a 5 per cent chance of acquiring a bacterial infection during a stay in hospital, and case-controlled studies have shown that the administration of antimicrobial agents during a stay in hospital, is a significant risk factor for infection with a resistant bacterial pathogen. The use of antimicrobial agents outside of hospitals, for example in nursing homes, day care centres and in animal feed to enhance food production, increases the selective pressure for resistant organisms to emerge. The use of broad-spectrum antimicrobial agents and prescription of antimicrobial agents in general for common conditions for which their effectiveness is unclear, and must be more dependent on the advice of medical microbiologists, possibly through Health Authority guidelines.

6.3 *Prescription of antimicrobial agents as a contributory factor*

6.3.1 While appropriate antimicrobial drug administration has unquestionable benefit, the clinical use of these valuable drugs is often inappropriate and may simply be prescribed to placate patients. For example, General Practitioners often prescribe antimicrobial agents for "Flu" or upper respiratory tract infections such as the "common cold". Although they may be instances where bacterial infections secondary to these common viral infections warrant such prescription, more often than not, more harm than good is being done by such treatment. Inappropriate drug use also arises from an absence of a proper microbiological diagnosis or inadequate diagnostic criteria, unnecessary prescription of expensive broad-spectrum agents, and not following established guidelines or taking microbiological advice (ie from a Medical Microbiologist).

6.3.2 Due to a number of factors, not least of which is the critical state of the patient, antimicrobial agents are often used empirically, prior to receiving a report from the Medical Microbiology Laboratory, which may take three or more days to process. Predicting the cause of disease without a microbiological diagnosis is risky because one or more organisms may be involved or they may be bacteria that can be transmitted to other

patients. Such use of antimicrobial agents contributes to the development of resistance. There is also concern that new cost containment measures may also impede appropriate management of infections if agents can only be selected from those on a hospital pharmacy's list.

6.4 *Use of antimicrobial agents in animal husbandry as a contributory factor*

6.4.1 The reliability of antimicrobial agents for clinical use in humans is inevitably affected by the wide use of the same classes of antimicrobial agents used in animal husbandry, particularly for poultry, as growth promoters. This goes beyond the straight forward considerations of food safety and, because of the continuous circulation of bacteria between humans and animals, the use of antimicrobial agents in animals has to be considered in its medical context. Veterinarians believe that antimicrobial drugs prevent the growth of normal gut flora, thus releasing the nutrients to the animal, that would normally be consumed by the bacteria from ingested feed. The reality of this approach is that it is impossible to eliminate the normal flora of animals with antibiotics. Normal flora will simply undergo an ecological shift to either resistant strains of normal flora and/or different species of organisms resistant to the antimicrobial agents administered. The use of antimicrobial agents stimulates the circulation of resistance genes between bacteria that constitute normal flora and pathogens such that eventually, resistant mechanisms evolve in pathogens, depending on the prevailing selective pressures.

6.4.2 Use of antimicrobial agents of the same chemical class as those used in clinical medicine as "growth promoters" in animal feed, has led to the selection of bacteria resistant to clinically usable antimicrobials. In the view of many, antibiotics are a substitute for good husbandry and the best farms do not use antibiotics as growth promoters. Nevertheless, the food industry is likely to argue that a reduction in the use of antimicrobial agents as growth promoters will mean a rise in food prices.

6.4.3 Although resistant species of *Salmonella* have found their way into humans via the food chain, it has on the whole, been difficult to show that animal strains of bacteria that also colonise or infect humans, can cause clinical infection. Nevertheless, the passage of bacteria such as vancomycin-resistant *E. faecium* through the human digestive tract via food such as poultry, may give resistant animal strains the opportunity to pass resistant genes to colonising human strains. Antibiotic-resistant animal strains of bacteria may therefore serve as a source of resistance genes that are transferable to human strains. It has been postulated that the use of a glycopeptide antibiotic, avoparcin, as a growth promoter in poultry husbandry throughout Europe, has been a major contributor to the emergence of vancomycin-resistant *E. faecium*. The transfer of vancomycin-resistant genes into *E. faecium* that cause human infection and already possess resistance to many antimicrobial agents, has produced vancomycin and multiply-resistant strains that are resistant to all clinically usable drugs and cause infections that are impossible to treat.

7. RECOMMENDATIONS

7.1 *Applied Medical Microbiology-surveillance and molecular epidemiology*

7.1.1 Calls for greatly improved surveillance at national and international levels, linked to better documentation of antibiotic usage and the effect of resistance on clinical outcome are being made in the USA by the American Society for Microbiology, and their broad recommendations are equally applicable to the UK and Europe. The establishment of a nationwide system of mandatory reporting of drug-resistant pathogens would facilitate the monitoring of resistance trends and give Health Authorities the basis for establishing treatment guidelines. A surveillance system could be jointly run between Public Health Laboratories and Teaching Hospitals, to monitor and periodically publish resistance trends, possibly by setting-up an Internet Service.

7.1.2 The population genetics of resistant bacterial strains is incompletely understood, although their distribution appears to be highly variable. Resistance is sometimes due to a variety of strains or, alternatively, one or a small number of successful and usually epidemic strains predominate. This kind of information is vital if we are to track and understand the epidemiology of infections caused by multiply-resistant bacteria, and should be included as part of the microbiology of surveillance.

7.2 *Antimicrobial Chemotherapy and basic Medical Microbiology*

7.2.1 The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistance to current antimicrobial agents. This also requires an understanding of the mechanisms of resistance and their genetic basis, which is also linked to the population genetics that underpins molecular epidemiology. These aspects, that are centred on Medical Microbiology, but interlink with other disciplines such as Public Health, General Practice and Primary Care, should be high on the list of priorities for funding bodies such as the Medical Research Council and the Wellcome Institute, and for HEFCE funded research within Medical Schools.

7.2.2 The time required to develop and clinically evaluate new agents is such that it takes several years before any such agent is available for routine clinical use. The value of this type of work needs to be recognised by Medical School management and HEFCE. Medical School links with the Pharmaceutical Industry should

be encouraged on a peer review basis rather than such links by medical academic and research staff being penalised. Research on risk factors, outcomes of infection, the microbiology of resistant organisms, new drugs and vaccines should be promoted. In the meantime, we are faced with increasing bacterial resistance to current antimicrobial agents.

7.3 Use of antimicrobial agents in animal husbandry

Last year, the European Union suspended the use of avoparcin on the grounds that it might promote resistance to vancomycin and teicoplanin, which are the last line of defence against MRSA. With few exceptions, such as topical iodine preparations, the use of any antimicrobial agent promotes the selection and therefore survival of resistant strains of infectious bacteria. In Europe, the amount of avoparcin used is measured in tons, compared to kilograms only of vancomycin and teicoplanin in humans. The selective pressure is heavily weighted towards animal use of avoparcin as the driving force in selection. It is therefore essential to establish a system within the Medical Control Agency so that the use and licence of antimicrobial agents in animal husbandry may be properly considered by Medical Microbiologists, Medical Scientists, as well as Veterinarians and the Pharmaceutical Industry. And this must be in conjunction with Europe.

7.4 Medical and General Education

7.4.1 Undergraduate and postgraduate medical education in the use of antimicrobial agents and treatment of infection needs to be strengthened within the broad remit of Medical Microbiology. Undergraduate medical curricula needs to take full account of Medical Microbiology, to include the microbiology, transmissibility and the special role of bacterial genetics, with respect to antimicrobial resistance and infectious epidemiology, infection control, sterilisation and disinfection, and medical practices that have microbiological consequences, and in particular, those that contribute to the emergence and spread of antimicrobial resistance.

7.4.2 Judicious use of antimicrobial agents should be promoted in continuing medical education and general professional and public education in the relevant aspects of medical microbiology. Key agencies such as the Department of Health, the Royal College of Pathologists and other medical colleges, the BMA, Institute of Biology, should all contribute to and develop broad educational systems to convey information to healthcare professionals, such as medical, Pharmaceutical, medical scientists, nursing and dental personnel; the General Public; Pharmaceutical and Healthcare industries; hospitals, nursing homes and other healthcare organisations involved with the care and treatment of patients; local and central government departments, elected officials and administrators.

Memorandum by J Hoare

1. This is a private submission made by a practising veterinary surgeon who qualified in 1965, began to study homoeopathy in 1988 and qualified as a veterinary member of the Faculty of Homoeopathy in 1993. It is based upon observations that I have made both before and after beginning my study of homoeopathy.

2. The problem of bacterial resistance to antibiotic therapy can be minimised by moving away from the concept that only antibiotics can be used successfully to cure infections. Before studying homoeopathy I had realised that in many cases the use of antibiotics only gave a temporary cure. On many occasions relapse occurred.

Direct observation over the last nine years has shown me that true cures of bacterial diseases are more common when using well chosen homoeopathic medicines. In support of this statement I would like to point out that I spend approximately £27,000 yearly with my main veterinary drug wholesaler. Over the last 12 months I have spent a total of £311 on antibiotic injectable agents and tablets, and a further £260 on eye and ear preparations that contain antibiotics. The other £26,000 going on vaccines, dog and cat foodstuffs, bandages etc and anaesthetic agents. If necessary I can provide copies of the relevant accounts to substantiate this claim. My practice is as healthy as ever it was. If my methods were ineffective it would have collapsed.

3. The future of antibiotics is therefore as a treatment of last resort than the primary treatment of choice.

4. The role of the government and the NHS is therefore to eliminate the bias against complimentary therapies in the teaching hospitals and veterinary schools. In particular homoeopathy, acupuncture and chiropractic ought to be given a more positive support. The postgraduate study of homoeopathy and acupuncture should be encouraged. The routine prescribing of antibiotics in cases where there is no immediate danger to the patient should be discouraged.

J Hoare, BVSc, MRCVS, VetMFHom

Memorandum by the Hospital Infection Society

1. I am writing as Chairman of the Hospital Infection Society in reply to your invitation for written submission on the subject of Antibiotic Resistance. By way of introduction, the Society is a leading Organisation in the field whose members seek to improve understanding of how Hospital Acquired Infections occur and of development of methods for their prevention. The Society has over 600 members the majority of whom are Medical Microbiologists in the UK.

2. We have carried out two major prevalence surveys of Hospital Acquired Infection (HAI) the most recent of which (1994) involved study of 37,000 patients in 157 hospitals. The prevalence of HAI was nine per cent. Infections involved the urinary tract, surgical wounds, lower respiratory tract and skin (66 per cent of the total). This and other similar surveys of HAI highlight the major morbidity and economic burden attributable.

3. The relevance of the above to Resistance to Antimicrobial Agents is that increasingly these infections are caused by multiply antibiotic resistant bacteria. Prominent examples are:

Methicillin resistant *Staphylococcus aureus* (MRSA).

Glycopeptide Resistant Enterococci.

Multiply antibiotic resistant *Klebsiella*.

Clostridium difficile.

Drug resistant yeasts (fungi).

Multi-drug resistant *Mycobacterium tuberculosis*.

These and other resistant microorganisms are responsible for serious infections in debilitated and often immune compromised patients.

4. The Hospital Infection Society has established several Working Parties either alone or in collaboration with other Societies or the Department of Health which are addressing the questions: how can these infections be prevented from being spread in hospital and how can antibiotics be used most prudently in order to conserve them for future use. Shortly the Society will jointly publish a Working Party paper on the Control of MRSA in Hospital which will be a valuable contribution to the subject.

5. The Society advocates the audit of hospital infections due to antibiotic resistant organisms as well as audit of the use of antibiotics and to this end has co-produced through its members and with fellow societies and the PHLS the Document: Standards in Infection Control in Hospitals.

6. Because of the extensive use of potent broad spectrum antibiotics in hospitals the Society is concerned that every effort is made to educate medical, pharmaceutical and other clinical staff on how antibiotics should be used most prudently. In this regard we would welcome some National initiative to produce such Guidelines which could act as a framework for individual Hospital Trusts to develop their own policies.

7. The Society proposes that more funding is provided by research bodies and Government to investigate the subject of antibiotic resistance in hospitals and its relationship to antibiotic resistance in the community and in animals. The latter point is made because there is some concern that certain antibiotic resistant bacteria eg, glycopeptide resistant enterococci may originate from animals.

8. I am pleased to advise that the Society would be happy to give oral evidence to the Committee if called upon to do so; either Professor Gary French, St. Thomas's Hospital UMDS, myself or another nominee.

I hope these comments are helpful to the Select Committee in its consideration of this important subject.

Prof T R Rogers

Chairman of the Hospital Infection Society

30 September 1997

Memorandum by the Infection Control Team, North Middlesex Hospital

I welcome and support the setting up of this Sub-Committee. I would like to highlight the following concerns.

1. Tuberculosis

Compliance with treatment for patients with TB. There is a need for the Department of Health to set up an effective national system to ensure that out patients comply with anti-TB treatment. Mechanism of identifying high risk non-compliers needs to be set up and an effective system to ensure Directly-observed Treatment implemented in this group.

2. There needs to be National rather than local policies on immunisation and vaccination of school children especially with regards to TB.

3. MRSA

The numbers of cases of MRSA is increasing, yet no extra funding has been made available to deal with the problem. Although there are national guidelines, MRSA positive patients are often denied appropriate treatment because of their status. No patient should be refused treatment because of MRSA. This should be built into hospital contracts and be monitored. There needs to be an information/education programme on MRSA for the general public.

4. Health Education

There needs to be a programme of public education on the risks of hospitalisation and prevention of infection. The public needs to be informed and educated on basic infection control issues so that they can take an active part in preventing the spread of infection.

5. Antibiotic Resistance

There should be nation-wide surveillance of antibiotic resistance on the basis of which national recommendations should be issued. This would help reduce the level of resistance.

Dr Yasmin Drabu, MB ChB DCH FRCPATH

Consultant Microbiologist/Infection Control Officer, North Middlesex Hospital, London N18 1QX. On behalf of the Infection Control Team at the North Middlesex Hospital.

18 August 1997

Memorandum by the Institute of Biology

The Institute of Biology, as the independent and charitable body charged by Royal Charter to represent UK biologists and biology is well placed to respond to the above House of Lords consultation. Its ability to provide informed comment is further enhanced by more than 70 specialist learned life science societies affiliated to it, some of whom have formally contributed specific comments to this response, and others provided informal comment. As such, it is pleased to participate in this consultation.

SUMMARY

2. Generally both the incidence and type of anti-microbial is increasing. This is already incurring increased health care costs. Similarly there has been a rise in agricultural costs (through the agricultural use of antibiotics). There is also the likelihood of a real risk of ecological costs through the use of herbicide, pesticide and microbial resistance markers in genetically modified organism). Strict guidelines for the use of anti-microbial and anti-metazoan agents backed up by monitoring is essential *if* the aforementioned costs are to be avoided. Importantly the UK needs to develop a co-ordinated anti-resistance strategy and to promulgate its anti-resistance philosophy overseas (to counter overseas reservoirs of increasing resistance). Underpinning this philosophy should be the recognition that anti-microbial, pesticide and herbicide resistance all arise out of the same biological phenomenon: that of mutation leading to adaptation in a Darwinian way. As such "resistance" in the broadest sense reflects a fundamental property of life. Given the importance of health care, agriculture and the environment to both our species and society, and that each have a *fundamental* biological dimension, resistance issues should be of great concern to those making policy in these sectors. Given that the attention to resistance issues to date has not been sufficient to halt its increase both in incidence and type, it clearly follows that far more effort is required: the alternative is to accept future increases in health care, agricultural and environmental costs. Expenditure in formulating and implementing a co-ordinated anti-resistance strategy is therefore an investment in substantial cost-avoidance.

GENERAL COMMENTS

Antibiotics, pesticides and herbicides are powerful tools

3. Antibiotics, pesticides, fungicides and herbicides are powerful tools. There is no doubt that the former has alleviated human (and animal) suffering considerably, while all have contributed considerably (though not solely) to the increase in recent decades' food production. Equally it is likely that GMO technology will contribute to further enhancement of the human food supply required to meet the needs of the World's increased population of the 21st century.

Antibiotic, pesticide and herbicide production and use contributes significantly to the UK economy

4. The UK has a strong pharmaceutical and chemical base. The UK accounts for about 6 per cent of World pharmaceutical sales and is the fourth largest exporter of pharmaceuticals after Germany, and (narrowly) the USA and Switzerland. This sector is one of the largest contributors to the UK balance of payments and the

direct level of employment is some 80,000.¹ Secondly, the agriculture sector, whose productivity gains in recent decades have substantially benefited from the use of pesticides, fungicides and herbicides, not to mention antibiotics as growth promoters, contributes about £10 billion to UK GDP.² It is therefore economically important that a properly balanced and co-ordinated strategy for tackling resistance in its various manifestations is formulated, and in the UK interests that it takes a lead in formulating strategies overseas.

A considered strategy combating resistance required

5. Given the benefits alluded to in (3) and (4) it is important that any anti-resistance strategy is formulated in full consultation with the pharmaceutical and chemical industries. Though restriction is required, *inappropriately* restricting the use of antibiotics, pesticides and herbicides can do more harm than good. For instance:

- failing to apply the manufacturers' recommended dose of fungicides can encourage resistance³ by allowing more of the pathogen to survive. While these survivors may have not been able to withstand a full dose some of their descendants might. A similar phenomena can sometimes be seen when using pesticides, herbicides and antibiotics.
- noting that in some instances the use of antibiotics is the only effective treatment. An agricultural example is that of swine dysentery caused by the spirochete *Serpulina hydysenteriae*. An outbreak may affect up to 75 per cent of livestock with a mortality rate of 25 per cent. Besides proper sanitation measures, control relies on the use of antibiotics.
- noting that as growth promoters the use of antibiotics as feed additives enables animals to perform closer to their true genetic potential in terms of physical growth. We are not aware that resistance has developed due to this nutrient sparing effect, and while caution (and the precautionary principle concerns notwithstanding) it is important to note that improved efficiency of feed to animal tissue not only improves production but lowers waste including nitrogen and phosphorous production (which have their own environmental impacts) and improves land efficiency (as the turnaround of animals is quicker).
- banning antibiotics can lead to suffering. The year following the 1986 Swedish ban on oral antibiotics for pig production an extra 900,000 weaned pigs (of a population of four million) suffered from diarrhoea, mainly due to enterotoxigenic *E.coli* and swine dysentery. The same ban has also led to an estimated 15 per cent increase production costs.⁴

A holistic approach to resistance is required

6. The Institute of Biology welcomes the House of Lords Science and Technology Sub-Committee addressing the problem of resistance to antimicrobial agents. The Institute also welcomes the Sub-Committee willingness to address resistance in metazoans (multicellular organisms, not just microbes). However while the Sub-Committee is aware of the use of antibiotics as growth promoters, and antibiotic resistant genes as markers for Genetically Modified Organism, it is disappointing that the Sub-Committee's consultation briefing states that these areas "are not the main focus of this inquiry." The Institute of Biology recognises that the Government's Advisory Committee on the Safety of Food, and that the Advisory Committee on Novel Foods and Processes, are each respectively addressing these issues, but the issue of resistance requires a holistic approach and the Sub-Committee is currently best placed to engage in the preliminaries of such an enquiry.

Resistant microbes, pesticide and herbicide resistant organisms arise similarly

7. The issues which underlie this consultation are closely related to those of biodiversity and biotechnology. Fundamental to the driving forces of microbial (bacteria, viral, fungal, yeast, microalgal and protoctistan) diversity is the genetic constitution of these organisms, the environment in which they are found and their ecological interactions with other components of the biosphere. The result is an extraordinary richness of the microbial diversity (most of which remains to be explored) and a tremendous diversity of strains of metazoan (multi-cellular species). Resistant organisms arise initially due to mutation. This can be natural, as in the case of many (though not all) microbes, or artificial (such as through artificially altering a genome *ie* when inserting resistance markers in GMOs). Secondly, resistant organisms (by definition) thrive in an environment containing the chemical (whether it be a sufficient level of antibiotic, herbicide or pesticide) to which they are resistant by virtue that their non-resistant competitors are removed. Migration from areas of antibiotic-treated infection, or pesticide/herbicide sprayed crops, increases the chances of colonies of strains of antibiotic resistant microbes, or crop pathogens respectively, to survive so providing the possibility of reinfecting (or attacking crops at a later date). Because resistant microbes, pesticide and herbicide resistant organisms, arise similarly, so strategies reducing the promulgation of resistance will also be based on similar biological thinking. Furthermore given that a number of the same genes conferring resistance to antibiotics in microbes, or resistance to herbicides, are also used as GMO markers, it would be by far more cost effective for there to be some co-ordination of tactics to counter resistance (be it resistance to antibiotics, pesticides

or herbicides) at a strategic national level. The alternative would be for a proportion of duplication of effort and, indeed, the possibility of conflicting strategies which both separately and together would engender unnecessary cost.

8. That many of the companies that manufacture antibiotics also manufacture pesticides and herbicides (or their cousin subsidiaries belonging to the same multinational) is yet another reason for employing a holistic and strategic approach to combat resistance in its broadest sense.

SOME RECENT (1997) DEVELOPMENTS ILLUSTRATIVE OF RESISTANCE ISSUES

Drug resistant pathogens in food of animal origin

9. In January WHO (World Health Organization) voiced concern over drug resistant pathogens in foods of animal origin⁵. It cited a form of food poisoning, human salmonellosis, and noted that costs of outbreaks in N America and Europe ranged from around US\$60,000 to over US\$20 million. Furthermore, a multi-drug resistant strain of *Salmonella typhimurium* (DT 104) emerged in 1988 in England and WHO noted that this multi-resistant is likely to retain its resistance even when antimicrobial drugs are no longer used. Though this is not a typical example, the lesson to be learned is still true—the message being that we must use antimicrobials carefully for if unnecessary use (or mis-use) encourages drug resistance and it may be subsequently difficult for strains to lose their resistant abilities even after antibiotic use has ceased.

Gene flow observed from transgenic crops

10. A recent paper (30 October) in *Nature*⁶ reported how genetically modified oilseed rape (*Brassica napus*) containing the *bar* gene conferring resistance to the herbicide Basta (glufosinate ammonium) and that this was passed to a weed (wild radish, *Raphanus raphanistrum*). Fortunately gene transmission decreased with successive generations, nonetheless the finding that such gene transfer has now been shown to be possible is cause for concern.

“Antibiotic use in food producing animals must be curtailed” says WHO

11. WHO announced on 20 October that, “excessive use [IoB emphasis] of antimicrobials, especially as growth promoters in animals destined for human consumption, presents a growing risk to human health and should be reduced.”⁷ WHO also said that they, “will work to integrate resistance monitoring in food animals and food of animal origin with its on-going programme of antimicrobial resistance monitoring of bacteria that cause human disease.” This philosophy is in line with the Institute’s view that any anti-resistance strategy must be holistic (see paragraphs 2, 6 and 20), though some may query the details behind this WHO release.

Prediction of Vancomycin resistant Staphylococcus aureus comes true

12. Since the 1980s vancomycin has been the last uniformly effective antibiotic available for the treatment of serious *S. aureus* infections. Methicillin resistant *S. aureus* (MRSA) outbreaks have become increasingly common. Such has been the concern over MRSA, and the recognition of the increase in antibiotic resistant micro-organisms, that one letter (of a cluster on the subject) published in the *British Medical Journal* this summer) noted that “if . . . [UK hospitals] abandon the infection control policies that have been set up for MRSA we leave ourselves with no defences against the spread of vancomycin resistant *S. aureus* when it emerges—as surely it will.”⁸ Then just three months later (September) the *BMJ* announced that a strain *Staphylococcus aureus* with increased resistance to vancomycin had been reported.⁹

SOLUTIONS

Adherence to infection control procedures

13. In addition to its own Sector of Biology Committees, the Institute of Biology is pleased to have received evidence, both formally and informally, from a number of its Affiliated Societies. The UK National Committee for Microbiology (which includes representatives from a number of Institute of Biology Affiliated Societies) has noted that the increased resistance levels in hospitals appears linked to the use and misuse of antibiotics, as well as the adherence to infection control procedures by hospital staff.

Perception that some hospitals have worthy local policies on antibiotic usage and the handling of emerging resistant strains

14. The British Electrophoresis Society has noted that many hospitals have a local policy on the prescription of antibiotics. The Institute of Biology considers that such local strategies should be part of a national holistic strategy (see paragraphs 2, 5 and 6). While the Institute of Biology does not have the remit to define such a strategy, it notes that the Pharmaceutical Sciences Group (an IoB) affiliate has contributed

to the Royal Pharmaceutical Society of Great Britain's response to this House of Lords consultation document and the Institute of Biology welcomes its recommendations. Such policies should be part of an overall resistance strategy.

Perception that industry will produce new drugs

15. The British Electrophoresis Society notes that one common perception within the health service is that pharmaceutical companies will continue to produce new antibiotics for economically well-off countries. The Institute of Biology is aware that in some quarters there is such complacency, but notes that unless standard professional practices are developed to minimise resistance, then it will continue to arise. While the Institute recognises that antibiotic discovery programmes will continue within the pharmaceutical industry, it expects breakthroughs regarding how drug resistance works following bacterial genome sequencing, and that while such breakthroughs will undoubtedly be economically important (and for the UK), they can only be considered as temporary gains in the absence of a well-considered and properly implemented and monitored strategy. Furthermore the pharmaceutical industry research effort is done primarily on unnaturally "pure" strains of micro-organisms, so that the effects of biodiversity: the existence of genetically similar, though critically different, organisms are often unsuspected and unpredictable.

New anti-viral drugs now meeting viral resistance

16. Of relevance to the above, the past few years have witnessed the emergence of a new brand of antimicrobial treatment—anti-viral drugs (such as amantadine against influenza). Yet already viral resistance is emerging (including against amantadine). One editorial article in the *BMJ* predicted that, "by early in the next century, antiviral drugs will have assumed an importance similar to that held by antibiotics over the previous 50 years," and recommended we prepare to counter the continued emergence of resistance.¹⁰

Where no controls on antibiotics exists so resistance flourishes

17. As the UK National Committee for Microbiology notes, the increased levels of antibiotic resistance in hospitals appears to be linked to their mis-use. Related to the Royal Pharmaceutical Society's own response to this consultation that antibiotic monitoring systems are introduced and that they be only available to patients following a proper consultation with a pharmacist or medical practitioner (RPS response paragraph 31), the Institute of Biology has received evidence illustrating the consequences of mis-use. Romania in common with a number of Eastern European countries (and many non-European countries) has no policy on antibiotics: antibiotics are available without prescription and self-administered, often without completion of the course and/or for the wrong ailments (eg viral infections). One Romanian dentist has informed this Institute that the administration of ampicillin fails to be effective in up to 30 per cent of cases. Nonetheless antibiotics remain a useful treatment in Romanian health care.¹¹ This underlines the need for the UK to promulgate overseas any anti-resistance strategy it formulates (see paragraph 4).

Review of World agriculture reveals many-fold growth over three decades in crop pathogen resistance

18. Gordon Conway's review of World agriculture (based on his panel's report for the Consultative Group on International Agriculture Research) just published this autumn shows how resistance to pesticides has grown in recent decades. Whereas in 1950 there were less than 20 species of arthropod (mainly insects) resistant to one or more pesticide, by the late 1980s this number had increased by over 21 fold to over 420. Over the same time the number of resistant strains of plant pathogens (mainly fungi) had increased from under 10 to over 50, and weeds from none to about 50.

RECOMMENDATIONS

19. (i) A strategy is required to deal with "resistance" and its various manifestations as identified by the House of Lords consultation "request for evidence" paper. Without a strategy resistance (be it resistance to antibiotics or to agricultural pesticides, fungicides and herbicides) will increase, as will the commensurate costs to society. Such a strategy must (among other elements) include:

- reference to the current situation of inappropriate antibiotic prescribing;
- support for the appropriate scientific infrastructure: the Public Health Laboratory, and hospitals and universities engaging in research and tackling resistance issues;
- an emphasis on food safety and other measures that reduce the need for the use of antibiotics;
- encouragement for using non-antibiotic resistant or non-herbicide resistant markers in GMOs (fluorescent markers are one such alternative); and
- reference to the appropriate use of pesticides, herbicides and fungicides within integrated pest management.

20. (ii) Given the inter-related nature of antibiotic and crop pest resistance, both in terms of biology and human organisations, various tactics need to be incorporated into a single strategy to meet the above (paragraph 19) goals. A single strategy will be both more effective and cheaper if the dimensions (primarily health, GMO and agricultural) were properly co-ordinated and monitored.

21. (iii) Such a strategy needs to be promulgated overseas which would otherwise act as reservoirs of increasing resistance.

22. (iv) Support for research is required. (This is part of a general requirement for extra scientific research to meet the problems of the increased World population of the next century.) While industry will continue to research into the biology relating to resistance, greater understanding of microbiology diversity, and species interactions is required.

FURTHER INFORMATION

23. In line with Government policy on openness, the Institute of Biology is pleased to make this consultation response publicly available. As such the Institute will shortly be placing this response on the World Wide Web. Queries relating to this and other IoB (science policy) responses should in the first instance be directed to Jonathan Cowie at the Institute of Biology, 20-22 Queensberry Place, London SW7 2DZ.

REFERENCES

1. Office of Science and Technology (1995) *Technology Foresight 4—Health and Life Sciences*. HMSO: London.
2. Office of Science and Technology (1995) *Technology Foresight 11—Agriculture, Natural Resources and Environment*. HMSO: London.
3. Brent K J, (1995) *Fungicide resistance in crop pathogens: How can it be managed?* Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques: Brussels.
4. McOrist S, & Lawrence K, (1997) *Briefing document for the Institute of Biology Submission to the House of Lords Committee on Antimicrobial resistance*. Personal communication.
5. WHO (1997) *Multi-drug resistant Salmonella typhimurium*. Fact sheet 139. World Health Organization: Geneva.
6. Chevre A-M, *et al* (1997) Gene flow from transgenic crops. *Nature* vol 389 p924.
7. WHO (1997) *Antibiotic use in food-producing animals must be curtailed to prevent increased resistance in humans*. Press release WHO/73. World Health Organization: Geneva.
8. Loudon K, & Burnie JP, (1997) Constant vigilance is needed to halt the emergence of resistance to vancomycin. *BMJ* vol 315, p59.
9. Josefson D, (1997) Vancomycin resistant *S. aureus* reported. *BMJ* vol 315, p700.
10. Pillay D, & Geddes AM., (1996) Antiviral drug resistance. *BMJ* vol 313, p503-4.
11. Hupov D, (1997) *Antibiotics*. Personal communication.
12. Conway G, (1997) *The Doubly Green Revolution: Food for all in the 21st century*. Penguin: London.

1 December 1997

Memorandum by Professor Keith Klugman, Pneumococcal Diseases Research Unit, South Africa

1. Thank you for the opportunity to present evidence on the rise in antimicrobial resistance worldwide and in particular its impact on the United Kingdom. I am the Director of the South Africa Institute for Medical Research and in addition I am Director of the SA Medical Research Council/SA Institute for Medical Research/University of the Witwatersrand Pneumococcal Diseases Research Unit. As the pneumococcus is the most important bacterial cause of pneumonia and meningitis which are priorities of this committee and as my Unit has conducted seminal research in this area I will confine my comments to changing patterns of resistance in the pneumococcus.

2. The first description of high level resistance amongst pneumococci, as well as multiple resistance (resistance to three or more classes of antibacterial agents) was in South Africa during 1977–78. These events prompted editorial comment in the *Lancet* and the *New England Journal of Medicine* and the Centers for Disease Control in Atlanta sent out Dr Joel Ward to conduct an investigation of the epidemic in collaboration with members of our Institute. The origin of the resistant genes was not clear at that time but subsequently evidence has come to light that the betalactam resistance is probably due to the transfer by means of homologous recombination of resistant genes from related bacterial species such as the oral streptococci which are invariably found in the mouths of humans.

3. The initial epidemic in South Africa was nosocomial. The initial epidemics of resistant strains in the UK were also nosocomial and in that instance the strains were thought to have come from Spain.

4. Features of the expanding epidemic include our documentation during the 1980s of the spread of resistant strains into the community. We further showed in a short report in the *British Medical Journal* that there was an association between patterns of antibiotic resistance and the patterns of antimicrobial use in different communities. An example of this is that penicillin-resistance was common in children attending day-care centres in Soweto where betalactams are widely prescribed. In contrast children living in more affluent areas of Johannesburg showed widespread carriage (18 per cent) of erythromycin-resistant strains in that community where erythromycin is often prescribed by general practitioners.

5. There are now good data to show an association between antimicrobial resistance in the pneumococcus and the use of antimicrobials at a national, regional, hospital and individual level.

6. An emerging problem associated also with antimicrobial resistance in the pneumococcus is that of HIV infection. HIV infected individuals tend to have more exposure to hospitals and more exposure to antimicrobials, thus increasing their risk of infection with resistant strains. In addition we have recent evidence that the paediatric serotypes of pneumococci which are more often antibiotic resistant preferentially infect HIV-infected adults, suggesting that their immunity to these paediatric types has been destroyed by the impact of HIV on their immune system.

7. An important aspect of the epidemiology of drug-resistance in the pneumococcus has been our recent ability to detect clones of pneumococci. On behalf of the International Union of Microbiological Societies, I will be convening a workshop which will include key role players from many countries including the UK, to define a system of nomenclature for these clones. With regard to the United Kingdom, it is clear that a number of clones originating in Europe, particularly in Spain are circulating in the United Kingdom and contribute a large proportion of the burden of antimicrobial resistance in the pneumococcus in your country. In addition there is evidence of a macrolide-resistant clone of serotype 14 which has been recorded by the PHLS at Colindale.

8. Strategies to reduce the burden of antimicrobial resistance will include an enhancement of surveillance, increased education of doctors in terms of rational use of antimicrobials with the implementation of guidelines for appropriate therapy, and education of the public to reduce demand for inappropriate use of antimicrobials.

9. There are at least two specific interventions which we are currently investigating. The first is the question of the impact of dose, type of antimicrobial and duration of therapy on the normal flora of the patient. Antimicrobial therapy has up to now had end points only related to the well-being of the patient, eg clinical cure, duration of hospitalisation. Studies are urgently needed to document the impact of various antimicrobials on the resistant nasopharyngeal flora.

10. Finally there are provisional data on the impact of pneumococcal conjugate vaccines on the carriage of pneumococci. There are data from The Gambia and from Israel suggesting that pneumococcal carriage can be reduced and the Israelis suggest that there may be an impact on antimicrobial resistance. We are currently concluding a large study involving 500 children in which more definitive answers to these questions may be provided. It is likely that the code for this double-blind study will be broken during the last quarter of 1997.

11. I hope that this submission is of some use to the committee and would be prepared to make verbal presentations and answer questions should this be required.

Professor Keith P Klugman

Director: The South African Institute for Medical Research. Director: The Medical Research Council/The South African Institute for Medical Research/The University of the Witwatersrand Pneumococcal Diseases Research Unit.

28 July 1997

Memorandum by Mrs L H Lewy

1. My husband was subjected to major surgery at our local hospital and his initial stay there was from late October 1988 to the end of January 1989.

2. During this time *The Observer* published an article on the prevalence of MRSA of which I attach a photocopy. You will see that the information is contributed by Edgware General Hospital's own consultant microbiologist, Dr Sanderson.

3. After my husband's (very poor) recovery from surgery he was repeatedly recalled to the hospital's Outpatient department for "checkups" where we waited, often for hours, in the company of patients from local long-stay hospitals (ie immune carriers of MRSA).

4. It was inevitable that sooner or later my husband would be infected by these carriers, and in February 1991 this did indeed occur. My husband incubated MRSA and within two weeks was dead of Pneumonia.

5. Fortuitously, death occurred in hospital, his GP having referred him for "physiotherapy (to help his breathing) over the weekend."

6. I was informed that “there would have to be” a post-mortem. (Later discovered to be a coroner’s post-mortem under the so-called “24 hour rule” which does not exist).

7. Over the weekend I recollected the likelihood of MRSA infection and contacted the Public Health Laboratory Service and discussed the question with various individuals. I also wrote a note asking for MRSA to be investigated (together with *Escherichia*, *Klebsiella*) in the contents of the lungs, and handed it in to the Pathology Department of the hospital before opening of business hours (ie there was no one there to speak to) on the Monday morning.

8. The post-mortem took place on the Tuesday and the hospital ignored my instructions. The hospital pathologist signed a report stating that death was “Lobar-Pneumonia: Natural Causes” and the coroner’s staff refused me an Inquest, and urged me to dispose of the body.

9. Subsequently I did a lot of telephoning around and ultimately found myself talking to someone who expressed great surprise at anyone’s having any information about MRSA, and when I said I had read about it in the papers, told me cheerfully “never to believe what I read in the press.” He—when I obtained a copy of the article—turned out to be the Dr Sanderson who had contributed the information to *The Observer*.

10. Quite apart from the circumstances surrounding my husband’s last years (delayed referral by GP, textiles retained within the wound after questionable surgery, poor post-operative treatment, etc, etc) I continue to protest about the actual events leading directly to his death, that is, repeated recalls into infected and infective surroundings in the Out-Patients Department.

11. The hospital has attempted to dispose of me by claiming that “it would be impossible to screen all patients being bussed in from the long-stay hospitals.” But it would be perfectly feasible either to take staff to the long-stay hospitals to provide whatever check-ups on site, or to arrange for vulnerable and debilitated “acute” patients (such as the hospital had made my husband) to be seen elsewhere, in a “clean” Out-patients Department.

12. I am well aware that the events I am relating took place almost ten years ago, but that MRSA may well by now be a “fact of life” everywhere—perhaps even in the private sector. But at the time (1988–1991) proper attention paid to the MRSA problem—bearing in mind that the hospital’s own microbiologist was fully seised of the facts and of their significance—steps could have been taken to protect vulnerable people from MRSA instead of cutting short my husband’s life just at a time when we were beginning to feel he was at last on the road to recovery.

13. I continue to question why, when I was approaching this matter from a Public Health aspect, no one was prepared to provide any concise or consistent information.

Why the coroner (or some unnamed and probably unqualified individual in the coroner’s offices) was prepared to accept the post-mortem “report” signed by an interested-party pathologist, and to ignore the protests of the Next of Kin and Personal Representative of the Deceased.

You will see that both the hospital and the Public Health Laboratory Service are implicated in turning their backs on the question of MRSA though I was speaking explicitly of this infection to all those whom I contacted. (Your (iv).) I will be happy to look out and provide you with contemporary documentary evidence of all the above.

Mrs L H Lewy

17 September 1997

Memorandum by the Medical Research Council

PREFACE

1. The Medical Research Council (MRC) is a body established by Royal Charter. This gives it an important and valuable freedom, in pursuit of its mission, to decide its scientific strategy and what research should be funded, taking account of scientific opportunities, health needs and opportunities for wealth creation. It is largely publicly funded and is accountable to Parliament and to the public for the work that it does. It has a special responsibility to work closely with users of its research output, especially the Health Departments, and to take account of their needs. The breadth of the MRC’s scientific programme is set by its mission to support research which aims to maintain and improve human health. It integrates research directly relevant to clinical practice and health service provision with basic research in the biological and other sciences.

2. Infection due to bacteria, fungi, viruses, protozoa and helminths is a major burden to health and health care services throughout the world. Infectious disease can be severe and ultimately fatal, as for example with AIDS and malaria. The continual appearance of new threats, or the increased prominence of existing infectious agents, which cannot yet be adequately controlled, make studies of infection a high priority for public health organisations and industry. Research on infectious organisms can be largely categorised as follows:

- basic genetic, molecular and immunological studies of infectious organisms;

- mechanisms of pathogenicity and identification of novel vaccine and drug targets;
- mechanisms of drug resistance;
- clinical (patient-based) studies (include health services research);
- development of new therapeutic approaches and preventative measures;
- evaluation of drugs and vaccines in animal models and clinical trials;
- epidemiology of infectious diseases and the identification of particular risk groups; and
- behavioural studies.

3. Target organisms/diseases of national and international significance include meningococcal meningitis, invasive pneumococcal disease, respiratory syncytial virus (RSV), chlamydia, tuberculosis, HIV and malaria. The threats to particularly vulnerable groups (eg elderly and immunosuppressed patients) are also important concerns.

RESISTANCE TO ANTIMICROBIAL AGENTS

4. Improved hygiene, the development of vaccines and the use of antibiotics have reduced the incidence of bacterial infections substantially during the 20th century, particularly in the developed world; the increasing use of antibiotics since the 1940s has also of course reduced the severity of those infections which do occur. The widespread use of antibiotics together with the length of time over which they have been available, have, however, led to major problems of drug resistant organisms. Resistance is also an important problem in dealing with viral, fungal and parasitic pathogens, even though antimicrobial treatment for viruses is still relatively new. The changing patterns of society and of the environment are leading to the re-emergence of old pathogens and to infection caused by new agents. Another increasing problem is opportunistic infection, by organisms that the body can normally fight off, the immune system is weakened or suppressed, for example due to AIDS or the use of immunosuppressive drugs to prevent the rejection of a transplant, or following serious trauma. Industry has a strong interest in identifying features of the basic biology of pathogens which might serve as new targets for anti-microbial agents, and in exploring new classes of drugs which can counter the threat of drug-resistance.

MRC'S RESEARCH

5. The MRC invests over £60 million each year across all areas of immunology, infection, and inflammatory diseases. In infections, the MRC's portfolio includes major, long-term programmes of work on the basic molecular biology, metabolism and pathogenesis of infectious organisms. The Council also supports basic studies on the prevalence and natural history of infectious diseases. This research underpins more applied work on anti-microbial drug resistance and the development of new drugs and vaccines. Most new drug development is done by industry, and MRC's involvement in this area is small.

6. Research which specifically addresses anti-microbial drug resistance is a relatively small part of MRC's overall portfolio (£0.3 million in the 1995–96 financial year). The research topics include:

- factors influencing the accumulation of antibiotics in Gram-positive bacteria;
- structural studies of key enzymes within drug-resistant and non-resistant HIV;
- resistance to beta-lactam antibiotics in *Neisseria*; and
- clinical studies of multiple combination antiviral chemotherapy regimens in HIV infection.

The current scale of research in part reflects the capacity of the academic science base to develop high quality research proposals. MRC's view is that there is potential to develop more high-quality work on resistance in the UK, and will shortly be developing plans for an interdisciplinary workshop (with Department of Health) on resistance, to explore the ways in which academia might complement the efforts of industry.

7. However, the challenge which drug resistance poses for health care cannot be addressed simply by research into the mechanisms of resistance to existing drugs. A broader approach is needed, to underpin the development of entirely new classes of drugs, to identify ways of preventing transmission, and new vaccines and other means of strengthening immune responses.

FUTURE RESEARCH

8. MRC will continue to conduct long-term research on the basic molecular biology, metabolism and pathogenesis of infectious organisms to underpin work on treatment and prevention. There are also a number of important opportunities for research into treatment and prevention, and opportunities for advancing our basic understanding of pathogens more rapidly, and these need to be developed by the science base and industry in collaboration. Promising areas include:

- the immunology of infectious diseases;
- sequencing of pathogen genomes;

- the development of new improved vaccines;
- targets for chemotherapy/new chemotherapeutic agents; and
- cheaper, more effective diagnostic agents.

Vaccine research and development

9. It is widely accepted that immunisation is an effective and cost-effective means of controlling infectious disease, and that many deaths could be prevented if more effective vaccines and immunisation programmes were available. In view of the fact that resistance to even the most recently developed antimicrobial agents is likely to emerge with time, the development of new vaccines is a very important approach to combating the problem of drug-resistant “superbugs”. In veterinary medicine, vaccines offer a cost-effective and efficient way of protecting livestock and reducing reservoirs of infection in wild animals, thereby reducing the need for widespread use of anti-microbial agents.

10. Despite recent successes in the field, there is a pressing need to improve current vaccines and develop new ones, and over the next decade scientific and technical advances will greatly facilitate progress in this area. In view of the limited research resources, there is a need to develop national priorities and set targets for new vaccine products based on health needs and scientific opportunities.

11. In December 1994, the MRC together with Glaxo (now Glaxo Wellcome), the Biotechnology and Biological Sciences Research Council and the Department of Health, launched the Edward Jenner Institute for Vaccine Research, as a new, independent research centre. Its strategic research programme is directed at novel ways of enhancing the immune response to vaccination and at new routes of delivering vaccines, so providing the basis for industry to develop new vaccines.

12. We have also recently set up an Expert Group to consider the feasibility of developing a UK strategy for both human and veterinary vaccines and produce a report to the Health Departments, the MRC, and the Biotechnology and Biological Sciences Research Council (BBSRC). The Expert Group concentrated on national issues and needs but recognised the importance of global priorities. Of particular interest were the problems surrounding the development of vaccines for resource-poor countries which are judged by pharmaceutical companies to be of little commercial value. The group's report will be available toward the end of 1997. The overall aim of any UK strategy will be to adopt a co-ordinated approach which will strengthen the position of UK vaccine-related science and lead to improved commercial exploitation and availability of better agents for use both in the UK immunisation programme, and also for other countries.

13. The UK has a very strong tropical medicine research base, and is also strong in the fields of molecular and cellular immunology. We need to do more to capitalise on these strengths to produce more candidate vaccines against tropical diseases. The worldwide value—in terms of health, quality of life, and economic development—of cheap and effective vaccines for parasitic diseases would be especially high, given the inadequacies of existing control measures (eg control of insect carriers and antiparasitic drugs). MRC is supporting some promising lines of research on vaccination against malaria: scientists from the MRC's Laboratories in the Gambia and the London School of Hygiene and Tropical Medicine are carrying out clinical studies of possible vaccines, in co-ordination with industry.

Pathogen genome sequencing

15. The small genomes of bacteria and viruses can now be sequenced quite rapidly, and even parasite genome are many times smaller than the human genome. The ability to read the pathogen's entire genome will be enormously valuable in understanding how it invades the body, causes disease, and evades the immune system: it will also allow targets for new types of antimicrobial drugs or new vaccines to be identified more easily.

16. The Council welcomes the Wellcome Trust initiative that has been established to sequence the complete genome of a large number of pathogenic organisms (bacteria and parasites), including *Mycobacterium tuberculosis* and *Plasmodium falciparum*. The initiative aims to sequence 50 important pathogenic bacteria and 4.5 major parasites in the next five years using dedicated sequencing centres such as the one at Hinxton Hall and one or two other sites in France and the USA. The sequencing of pathogen genomes will have a substantial impact on research and will serve as a powerful stimulus to drug design and discovery and vaccine R&D. To avoid duplication, and to maximise effectiveness, the sequencing efforts of industry and academia will need to be well co-ordinated. We shall also need to promote close collaboration between the geneticists undertaking the sequencing, and other research teams with expertise in the organism's general biology and its interaction with the human body, to ensure best use is made of the new knowledge in advancing clinical practice and developing new treatments.

GENERAL BASIC AND CLINICAL RESEARCH APPROACHES

17. These new opportunities will be taken forward as part of broad programmes of multidisciplinary basic and clinical research. The following examples of current research in three key areas show the range of approaches being used.

Bacterial disease

18. The MRC's research interest in this field of bacterial infections is broad, encompassing mechanisms of pathogenicity and drug resistance, through to the host's response to infection and the identification of particular risk groups.

19. MRC's scientific strategy places particular importance on tuberculosis research. Tuberculosis is a major global health problem: it is estimated that one third of the world's population is infected with the causative organism, *Mycobacterium tuberculosis*, and the majority of these reside in developing countries. Despite the availability of effective chemotherapy, the incidence of tuberculosis is rising. Reasons for this include the impact of HIV infections, the development of drug resistant strains of *M. tuberculosis* and inadequate resources for TB control programmes in developing countries. Furthermore, the protective effect of BCG vaccine, which is the most widely given vaccine in the world, is variable (0 to 80 per cent depending upon the population considered) in its efficacy against tuberculosis. For these reasons, there has been a renewed research interest in tuberculosis, driven particularly by the need for more effective disease control measures, improved diagnosis and a more effective vaccine.

20. MRC supports tuberculosis and mycobacterial research in its own institutes and units, and through grants to universities and hospitals. In 1995–96 we invested about £1.4 million, which included studies of pathogenicity and virulence, bacterial dormancy and drug sensitivity, biosynthetic pathways and bacterial surface components as drug targets, protective immune responses and the control of infection by the host's immune system.

21. To give one example of the results obtained, scientists from the MRC National Institute for Medical Research in London have taken the first steps towards developing a new, and potentially more effective kind of TB vaccine—one made from DNA. The vaccine is made from copies of sections of DNA from *Mycobacterium leprae* (the infectious agent that causes leprosy and which is closely related to the one that causes TB). Mice injected with the DNA have been shown to have as much protection against infection with the related TB bacterium *Mycobacterium tuberculosis* as if they had received the traditional TB vaccine.

Viral infection

22. While increasing effort, worldwide, is being devoted to understanding the basis of pathogenesis and new approaches to prevention and treatment, at present there are few effective treatments, and the development of antiviral therapies presents a particular challenge to industry. Important viruses for health in the developed and developing world include HIV, hepatitis C, influenza, papillomavirus, herpesvirus, RSV, human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV). Although reasonable progress has been achieved in the control of chronic infections by anti-viral drugs (eg Zovirax for herpesvirus), improved agents are required for the effective treatment of acute viral infections.

23. To achieve the long-term goals of preventing and treating HIV infection and AIDS, the MRC has a many-pronged research strategy. One goal is to develop new anti-HIV drugs and vaccines in partnership with industry. Here, MRC supports basic research focusing on detailed studies of the molecular biology of the virus and the infected host cell with the aim of identifying new drug targets, to complement rather than compete with the pharmaceutical companies' activities in this area. The MRC has also been active in clinical trials to assess the efficacy of combinations of anti-retroviral drugs, which have helped shed light on the problem of resistance in HIV. Other important current (or planned) research includes development of vaginal virucides to help prevent transmission; evaluation of new drugs and combinations of drugs which may be more effective in prolonging life or avoiding development of resistance; and clinical studies of immunotherapeutic agents, also in association with industry.

Parasitic disease

24. The MRC's portfolio of long-term support for parasitology is centred on basic and clinical malaria research, particularly the immunology and biology of the parasite and the pathophysiology of infection. Malaria is the world's most important parasitic infection, causing disease in over 300 million people worldwide and over a million deaths each year. Most infections and deaths occur in Africa, among children, but malaria is common also in Asia and South and Central America. Each year, 2,000 people are diagnosed as having malaria in Britain; some die, more are seriously disabled. Resistance to commonly used drugs, like chloroquine, is increasingly widespread, and although effective new drugs are emerging from industrial research—such as Malorone (Glaxo-Wellcome)—simple and sustainable interventions against malaria are urgently needed.

25. Cerebral malaria has a mortality rate of 10–30 per cent despite treatment with parenteral quinine, a situation that may worsen with the spread of quinine resistance. Clinical research carried out by MRC scientists in the Gambia and Wellcome Trust scientists in Vietnam have shown that artemether, a drug derived from a plant used for centuries in Chinese herbal medicine, is as effective as conventional quinine in the treatment of malaria. This finding is highly significant given the decline in effectiveness of quinine treatment in parts of South-East Asia where the malaria parasite is becoming increasingly resistant.

26. MRC has also supported basic research into the factors that predispose some individuals to succumb to severe malaria, while others only develop mild disease. Understanding the reasons for the variability may help improve clinical practice, or provide opportunities for new treatments.

27. Finally, although, as mentioned above (13), vaccine research is promising, we still need improved methods for prevention. The effectiveness of insecticide treated bednets was first demonstrated by MRC in the Gambia and, under research conditions, they reduced childhood mortality by more than 60 per cent. However, operational constraints have limited their impact under normal conditions and alternative strategies are required to reduce prevalence. These may include gametocytocidal therapy given in combination with conventional anti-malarial therapy and adjunctive therapies for severe malaria.

G K Radda

15 October 1997

Memorandum from Professor D A Mitchison, St George's Hospital Medical School

DRUG RESISTANCE IN TUBERCULOSIS

1. Standard treatment of tuberculosis is with three first line antibacterial drugs: isoniazid, rifampicin and pyrazinamide. When drug resistance emerges to at least isoniazid and rifampicin, the strain of tubercle bacilli is called multi-drug resistant (MDR). There are great difficulties in treating patients with MDR strains as none of the alternative eight or nine antituberculosis drugs are as potent, and many of them are extremely expensive. The patient may become untreatable and die, while the cost of treatment is usually in excess of £100,000.

2. At present, there are few patients (probably fewer than 20) in the UK with MDR strains but the number is likely to rise, mainly because they are occurring with increasing frequency in other countries and are brought in by immigrants or by British citizens who are infected while travelling abroad. They are also caused by gross irregularity in drug taking in UK patients, especially by the alienated poor in big cities. MDR strains are highly infectious and can cause epidemics of virtually untreatable diseases. MDR tuberculosis is a serious and growing threat.

3. There are two approaches to reducing the MDR problem. The first of these is to prevent gross irregularity in drug taking (which causes MDR disease) by full supervision of the taking of all doses of drugs. Such a programme has reduced the prevalence of MDR strains in the big cities in the USA but is expensive. Full supervision could be carried out more economically if the doses of drugs could be given at wide intervals, for instance once a week. Clinical trials of the long-acting rifamycin, rifapentine, are proceeding at the moment both in Hong Kong (which I coordinate) and by the US Public Health Service in the USA. If successful these will allow once-weekly rifapentine/isoniazid to replace daily rifampicin/isoniazid. Nevertheless, even then, full supervision would remain an expensive programme.

4. The second way of dealing with the problem in the medium and long term is to develop new antituberculosis drugs as effective as the three first-line drugs and of reasonable cost. There has been little progress during the last 30 years in the development of alternative drugs. Rifampicin, the most recently developed of the three first line drugs was first synthesised in 1963. To the best of my knowledge, there is only one pharmaceutical company (GlaxoWellcome) in the UK with a programme aiming to develop suitable alternative drugs. Another pharmaceutical firm in the USA (PathoGenesis Corporation) is also attempting to do this. There are other small firms in the USA and Japan aiming to produce high cost alternative drugs useful in treating MDR patients but these are unlikely to solve the need for replacing first line drugs. Other large pharmaceutical firms have given up any attempt to produce new antibacterials specifically aimed at the treatment of tuberculosis.

5. The difficulty in the production of alternative first-line drugs is the high cost of development, particularly in its last stages when very large-scale clinical trials lasting several years are necessary. Much of the cost of these trials is artificially inflated because, increasingly, physicians, hospitals and medical schools ask the pharmaceutical companies to pay the entire cost of treatment of the patients despite the fact that they have, in any case, to be treated. Even when bodies such as the Medical Research Council (MRC) are prepared to fund some of the costs, they inevitably try to claw back much of the funding from the pharmaceutical companies. The result is often that the clinical trials are not carried out.

6. There is a mechanism in the USA entitled the Orphan Drug Programme which will help in the funding of clinical trials required for licensing requirements where there is little prospect of the profit margin on a new drug being remotely equal to the development costs. No such mechanism exists in the UK.

7. What is required are:

- (1) A Government-funded unit whose main aim would be to facilitate the development of new drugs and improve the use of those already in existence. Up until 1984, there were two MRC units, directed by Professor Wallace Fox and myself. These units played the major role in developing the treatment of tuberculosis on a worldwide scale. In 1994, a topic review of mycobacterial infections was made

for the Physiological Medicine and Infections Board of the MRC by a panel (chaired by Prof K McAdam), of which I was a member. As this report is confidential, I would suggest that the Select Committee approach the MRC to obtain a copy. The first of the principal recommendations was that "an initiative in clinical mycobacterial research (including links to field site/s in developing countries) is both timely and feasible". The topics that might be covered under the initiative included subjects relevant to drug development (preclinical drug testing, pharmacology, animal models of treatment), clinical trials, reference microbiology, epidemiology, surveillance and social aspects. These subjects are similar to those covered by the earlier MRC units. The growing MDR problem emphasises the importance of establishing a new clinical unit. As far as I am aware, no such unit is being established.

It is important that drug development and assessments be carried out by a unit which can have financial security in the long term. Support for clinical studies by project grants (whether MRC or Wellcome Trust) is unsatisfactory since initial funding may be provided but not continued despite the fact that a large-scale trial is proceeding. This is exactly what happened in the Hong Kong study of rifapentine for which MRC provided the initial support but declined to continue this support during the remainder of the study. Luckily, the Hong Kong Government was able to provide most of the financing that was necessary.

- (2) We need the equivalent of an Orphan Drugs Programme to help finance the development of new drugs.
- (3) There is already a good working relationship between the pharmaceutical industry and academic research institutions but this could be improved. Part of the difficulty is that the bodies that fund academic research tend to consider that the funding of drug development should be entirely financed by pharmaceutical firms. It is important to realise that the cost of clinical trials necessary for licensing a new drug is usually borne entirely by the pharmaceutical firm but they are then unable to fund further developmental studies, which may be highly desirable. The borderline between licensing and further development is often uncertain.
- (4) Further research in academic institutions should be encouraged as a high national priority, quite apart from the link to pharmaceutical firms. There are issues which are essential for understanding the fundamentals of drug action and for developing rapid diagnostic tests for MDR cultures. For instance, more research is needed on tubercle bacilli that are dormant, resist the action of antibacterial drugs and are responsible for the current six-month duration of treatment.

Professor Emeritus D A Mitchison
Department of Medical Microbiology

4 September 1997

Memorandum by Dr Jean Monro, Breakspear Hospital

The Breakspear Hospital has long been involved in the treatment of patients with environmental sensitivities, and I append information about the hospital and its status. Many of the patients who have attended here have had recurrent courses of antibiotics, and have become sensitive to other agents in the environment, including loss of oral tolerance. Oral tolerance is a state of specific immunological unresponsiveness induced by prior oral administration of antigen, and is antigen specific. The food sensitivities that people contract include sensitivities to yeast products in foods, particularly monosodium glutamate which is ubiquitously present as a flavouring agent in our diets, but also to yeasts from bread and other species of *Candida* which occur in the bowel. The debate in the population about *Candida* causing problems is hotly disputed in medical circles, and yet one cannot ignore patients' complaints that they are worse when they take a particular food containing yeasts, and their symptoms are worse after taking yet another course of antibiotics. This is attributable to a vogue for considering that *Candida* is a problem, but indeed there is now substantial evidence from a metabolic point of view that this is a real possibility.

What has been evaluated over the past months by us is the way in which the products of yeasts can be discerned in the urine. Some of these are extremely toxic, and we have been able to identify the toxic metabolites which, in effect, are mycotoxins, as well as the catabolic breakdown products of yeast which can inhibit metabolic function in humans. These effects are on the Krebs cycle where tartaric acid can affect the cycle at the point where malic acid is produced—see attached, and also arabinose cross links to proteins between the lysine and arginine residues. These proteins are unavailable for structural purposes and for the production of antibodies and enzymes, and they can in fact form neurofibrillary tangles in the brain similar to those seen in Alzheimer's disease, and there is some suspicion that auto-immune disease can be induced. Therefore, the cross linkage with arabinose/arabintol from fungi is a direct metabolic toxic effect which will also affect the immune system. There are other residues which can be discerned and many complex effects from the burden that yeast overgrowth plays.

We have been treating yeast overgrowth and Candidiasis here for some years, based on a belief in patients' symptoms, which is where medicine must start. Now that we have some explanations we would like this aspect of the side-effects of antibiotic therapy to be considered by your Committee.

More antibiotics are prescribed than any other item of prescription medication in this country. The inadvertent side effects on gut ecology are often not considered, and the consequent metabolic effects are therefore also not known or recognised widely by the medical profession. Is it not time that this is considered? Many of the recipients of antibiotics are children. Could this not constitute part of the reason for increasing sensitivity states? One in seven children has asthma, which is not just an effect of allergy to airborne particles or pollutants.

The data on our findings is available for the Select Committee to scrutinise and we would welcome a retrospective investigation of the findings we have made for patients, and also, if required, would be prepared to have a prospective study which can discern the prevalence of this problem in the population.

Jean A Monro MB, BS, MRCS, LRCP, FAAEM, DIBEM, MACOM, Medical Director, Consultant Physician Fachkrankenhaus Nordfriesland, Bredstedt, Germany

17 December 1997

APPENDICES (*not printed*)

- General information concerning Breakspear Hospital and its status.
- Information concerning *Candida*.
- Analysis of investigation of urinary organic acids and nutritional status in patients with diverse symptoms of intolerance to foods and chemicals.
- Explanation of urinary organic acids and their metabolic interaction from yeast.
- Overview of urinary organic acid references.

Memorandum by Monsanto Europe

Monsanto Europe appreciates this opportunity to provide information to the Select Committee on Science and Technology Sub-Committee I on Resistance to Antimicrobial Agents. At this time, we would like to provide comments on the specific topic of the use of antibiotic resistant markers in genetically modified organisms. Our comments will be brief since the Call for Evidence stated that the main focus for this inquiry was not the use of antibiotic resistant markers in genetically modified organisms and that this topic had already been recently considered by the Advisory Committee on Novel Foods and Processes.

When the use of antibiotic resistant markers in genetically modified organisms is being considered, it is important, for any risk assessment, to clearly distinguish the type of genetically modified organism in question. For example, this type and extent of risk may be different for genetically modified microorganisms compared to genetically modified plants. These differences have been discussed in a number of national and international fora including the recent joint FAO/WHO expert consultation, held 30 September–4 October 1996 (Biotechnology and Food Safety, RAO, Rome).

Our comments will specifically address the use of antibiotic resistant markers used for genetically modified plants, since Monsanto is actively involved in this area of biotechnology. Antibiotic resistant markers have been critically important in the development of many of the genetically modified plant products that are in the market and that have been developed to date. As clearly stated in the report from the joint FAO/WHO joint expert committee (1996) "Their continued use in plants remains critical to the production of genetically modified plants." There are limited alternatives today. Therefore, many of the genetically modified plant products that will be introduced into commerce in the foreseeable future will continue to contain these markers.

Most importantly, the safety assessments that have been carried out by international experts in this scientific field have repeatedly concluded that the use of antibiotic resistant marker genes in plants will not significantly impact either the frequency of antibiotic resistant microorganisms nor the therapeutic efficacy of the respective antibiotic for either human or animal applications.

This conclusion was reached by two independent scientific committees that were requested to provide specific advice to the European Commission. These committees were the Scientific Committee for Food and the Scientific Committee for Animal Nutrition. These committees were specifically assessing the food and feed safety of the products derived from a genetically modified, insect protected maize product that contained a *bla*-gene that confers resistance to the antibiotic ampicillin. The Scientific Committee for Food concluded that "The possibility that the product would add significantly to the already widespread occurrence of ampicillin resistant bacteria in animals or man is remote". The Scientific Committee for Animal Nutrition concluded that "(a) the possibility of transfer of a functional *bla*-gene construct is virtually zero and (b) that if the virtually impossible event occurred, it would have no clinical significance".

As the Select Committee is well aware, the United Kingdom Advisory Committee on Novel Foods and Processes (ACNFP) has also discussed this topic in detail and have provided guidance for assessing the safety of products containing an antibiotic resistance gene. While the ACNFP has raised concerns about particular uses of specific antibiotic markers, the ACNFP reached a general conclusion similar to that of the two standing committees mentioned above for genetically modified plant products, including a genetically

modified maize product that contained an antibiotic resistant gene encoding resistance to the kanamycin and neomycin antibiotics. The ACNFP concluded that the presence of this gene would not compromise antibiotic therapy and would not compromise feed safety of the unprocessed plant material.

Similar general conclusions have been reached during the 1993 WHO workshop on Health Aspects of Marker Genes in Genetically Modified Plant and the 1996 joint FAO/WHO expert consultation on Biotechnology and Food Safety.

Based on the information summarised above, the scientific consensus is that the impact of the introduction of genetically modified plants on the frequency of resistance to antimicrobial agents is likely to be negligible. It is appropriate, therefore, that the Select Committee on Science and Technology Sub-Committee I on Resistance to Antimicrobial Agents focus on areas more pertinent to the objective of addressing the rise in resistance to antibiotics and other antimicrobial agents and its implications for UK and international public policy.

If the Sub-Committee decides to address the specific topic of the use of antibiotic resistant markers in genetically modified organisms during this inquiry, Monsanto would appreciate the opportunity to provide additional evidence on this topic for the review by the Sub-Committee.

Stephen Walters,
Regulatory Affairs Manager, Monsanto Life Sciences Company

26 September 1997

Memorandum by Dr P Murphy, Director, Northern Ireland Public Health Laboratory

1. INTRODUCTION

This evidence is focused on the environmental release of the bacterial species *Burkholderia cepacia* as a biological control agent. In recent years agricultural microbiologists have developed this bacterial species for (a) distribution to enhance crop yields through its anti-fungal properties^{1,2} and (b) biodegradation of landfill waste sites and aqueous microcosms^{3,4,5}. The enthusiasm for these developments among agricultural scientists has not been tempered by their potential clinical effects realised in clinical medicine. Such environmental loading may present a significant threat to patients with Cystic Fibrosis for whom acquisition of this organism can significantly reduce life expectancy⁶. This organism in medical practice is commonly resistant to all available antibiotics. In those isolates which are not initially pan-resistant the development of total or pan-resistance develops rapidly. To my knowledge this issue is not being considered by either ACMSF or ACNFP.

2. CF BACKGROUND

Cystic Fibrosis is a commonly occurring genetic disease with a frequency in people of European origin of 1:1,600 to 1:2,300 live births. Respiratory infection is the complication of greatest significance with respect to morbidity and mortality. Several species of bacteria contribute to the eventual respiratory failure but *B.cepacia* has a particularly ominous prognostic implication. It is possible with good infection control to reduce the spread of *B.cepacia* to patients who have never acquired it.

3. B.CEPACIA BACKGROUND

B.cepacia, formerly recognised as a spoilage bacterium in onions, has been recognised as a highly significant pathogen in patients with CF. The organism has recently been proposed as a "*B.cepacia* complex" composed of five genomovars.⁷ These are: I; II (*B.multivorans*); III which is the main epidemic strain and 50 per cent of clinical adult isolates belong to this group; IV; and V (*B.vietnamiensis*). While it may prove in the future that some of these genomovars are more pathogenic than others, all have been found in patients with Cystic Fibrosis. The biopesticide is *B.vietnamiensis* or genomovar V.

4. IMPLICATIONS OF B.CEPACIA IN CF

4.1 Different centres have different degrees of colonisation rates in their CF patient population. This can range from 0 to 40 per cent of patients in each centre.

It is not known how the various genomovars of *B.cepacia* complex each contribute to the lung pathology in cystic fibrosis. We know that as a bacterial group they may either colonise with minimal pathogenicity, colonise or infect with chronic low grade infection, or in 20 per cent of patients can develop a *B.cepacia* syndrome involving a necrotising pneumonia and bacteraemia associated with a rapid clinical deterioration and high mortality. We have recently isolated it from blood cultures in a patient with cystic fibrosis in Belfast. Once acquired in the Cystic Fibrosis lung it is not possible to eradicate it.

4.2 Over the last decade it has therefore become routine to segregate CF patients into those with and without *B.cepacia*. In our recently opened adult Cystic Fibrosis Unit in Belfast we strictly segregate the two groups of patients into separate wards and have achieved complete success in preventing the emergence of *B.cepacia* to non-colonised patients over the last three years.

5. DEVELOPMENT OF *B.CEPACIA* AS A BIO-CONTROL AGENT

5.1 *B.cepacia* has been shown to act as an antifungal agent in order to avoid post-harvest loss of fruit and vegetables. Huang *et al* (1993)⁸ showed that spraying *B.cepacia* (1.6×10^9 cfu/ml) onto Washington navel oranges reduced post harvest loss mainly due to green mould decay. Freitas *et al* (1991)⁹ showed *B.cepacia* to have antifungal activity against *Rhizoctonia solani* and therefore an effective inoculant as a biocontrol agent of winter wheat. Parke (1991)¹⁰ showed that *B.cepacia* was an effective biological control of *Pythium* damping-off and *Aphanomyces* root rot of pea. Conversely *B.cepacia* has been shown to act as a pathogen in certain vegetables by causing soft root rot disease (Wiwut-Daenpsubha and Quimio, 1980).¹¹

5.2 Although there are some arguments to suggest the pesticide strains don't spread early in CF patients¹², nevertheless these bacteria clearly do present a substantial risk to patients for acquisition and infection, with an infection which is often totally resistant to all available antibiotics. As a member of the International Working Party on *B.Cepacia* we have discussed acquiring strains used in agriculture at our last meeting in October in the US but understand that agricultural sources have expressed some reservations and reluctance to engage in research on its impact in human infection as it might inhibit their development programme. Such reservations must be overcome and human health prioritised over agricultural economic advantage.

6. PROPOSAL

6.1 Molecular Epidemiology

Research should be carried out into the specific impact of releasing *B.cepacia* into the environment and on the effect this may have in the development of multi-resistant *B.cepacia* in Cystic Fibrosis.

1. Human clinical isolates should be collated and analysed both phenotypically (for *B.vietnamiensis*) and genotypically.
2. Agricultural bio-pesticide isolates should be similarly analysed.
3. Other common environmental sources and reservoirs eg agricultural soil, environmental waters should be sampled.
4. Molecular epidemiological analysis should be applied to *B.cepacia* isolates to assess commonality and epidemiological links between the environment and human clinical isolates. SSCP analysis and AP-PCR genotyping methodologies should be applied to help elucidate epidemiology and modes of transmission.
5. Presumptive identification of *B.cepacia* environmental strains by Sequence Specific Priming (SSP) of the 16S rRNA gene by PCR.
6. Sequential isolates should be followed genotypically and phenotypically to assess the development of pan resistance of this bacterium in human infection.

6.2 Novel therapeutic strategies

As *B.cepacia* human isolates are commonly resistant to all available antibiotics, there is a need for non-conventional approaches and research into the application of new and novel therapeutic strategies. This could include:

- (i) Bacteriophage.
- (ii) Peptide antibiotics.
- (iii) Phage display libraries.
- (iv) Synergy studies of antibiotics and non-antibiotics.

6.3 Research Commissioning

This work could be optimally commissioned by the Department of Health rather than the Department of Agriculture and Fisheries.

6.4 The N. Ireland Regional Cystic Fibrosis Units

The two units (paediatric and adult) in Belfast serve a stable CF population of over 200 and provide a particularly integrated clinical and laboratory collaborative team approach. There is an established focused programme of research on the molecular diagnosis and epidemiology of *B.cepacia* as N. Ireland is a region

with comparatively high prevalence of *B. cepacia* in the Cystic Fibrosis population. We would be particularly able and keen to develop, as part of our future research strategy, the investigation of epidemiological reservoirs of *B. cepacia*, particularly with an emphasis on the issues encompassed in this evidence and the use of *B. cepacia* as a bio-pesticide and its potential risk to morbidity and mortality in human Cystic Fibrosis.

REFERENCES

- 1 Homma Y, Sato Z, Hirayama F, Kanno K, Shirahama H, Suzi T. Production of antibiotics by *Pseudomonas cepacia* as an agent for biological control of soilborne plant pathogens. *Soil Biol Biochem* 1989; 21: 723-728.
- 2 Fridlander M, Inbar J, Chet I. Biological control of soilborne plant pathogens by a β -1,3-glucanase-producing *Pseudomonas cepacia*. *Soil Biol Biochem* 1993; 25: 1211-1222.
- 3 Bhat MA, Tsuda M, Horike K, Nozaki M, Vaidyanathan CS, Nakazawa T. Identification and characterisation of a new plasmid carrying genes for degradation of 2,4-dichlorophenoxyacetate from *Pseudomonas cepacia* CSV90. *Appl Environ Microbiol* 1994; 60: 307-312.
- 4 Havel J, Reineke W. Degradation of Aroclor 1221 in soil by a hybrid pseudomonad. *FEMS Microbiol Lett* 1993; 108: 211-217.
- 5 Krumme ML, Timmis KN, Dwyer DF. Degradation of trichloroethylene by *Pseudomonas cepacia* G4 and the constitutive mutant strain G5 223 PRI in aquifer microcosms. *Appl Environ Microbiol* 1993; 59: 2746-2749.
- 6 Lewin LO, Byard PJ, Davis PB. Effects of *Pseudomonas Cepacia* colonisation on survival and pulmonary function of Cystic Fibrosis patients. *J Clin Epidemiol* 1989; 43: 125-131.
- 7 VanDamme P, Holmes B, Vancanneyt M, Coenye T, Hoste B, Coopman R, Revets H, Lauwers S, Gillis M, Kersters K, Govan JRW. Occurrence of multiple genomovars of *Burkholderia cepacia* in Cystic Fibrosis patients; Proposal of *Burkholderia multivorans* sp nov. *International Journal of Systematic Bacteriology* October 1997.
- 8 Haung Y, Deverall, BJ, Morris, SC and Wild, BL (1993). *Post Harvest Biology and Technology*, 3, 293-304.
- 9 Freitas JR de, Germida JJ and De Freitas JR (1991). *Canadian J Micro*, 37, 780-784.
- 10 Parke JL (1991). *Bulletin-SROP*, 14, 30-33.
- 11 Wiwut-Daengsubha and Quimio AJ (1980). In: *Proc of the 2nd Southeast Asian Symposium on Plant Diseases*, Kasetsart University, Bangkok.
- 12 Govan JRW, Hughes JE, Vandamme P. *Burkholderia cepacia*: medical, taxonomic and ecological issues. *J Med Microbiol*. 1996; 45: 395-407.

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24 December 1997

Memorandum by the National Anti-Vivisection Society

BACKGROUND

1. The discovery and large-scale production of penicillin, some half a century ago, heralded the dawn of the "antibiotic era". However, less than 10 years later, strains of *Staphylococcus aureus*, a bacterium which causes boils and more serious infections had acquired resistance to this new wonder drug¹. Initially these resistant strains were confined to hospitals (nosocomial infections) but soon spread to the community. As novel antibiotics were discovered, bacteria evolved strategies to overcome them: by modification of the target to decrease its susceptibility; by enzymatic inactivation of the antibiotic, for example by β -lactamases produced by penicillin-resistant strains; or by reduction of drug transport into the cell. These resistance strategies are mediated either by chromosomal mutation or by the incorporation of a transmitted element, such as a plasmid or transposon^{2,3}. The rise in resistance to antimicrobial agents has caused concern among the scientific and medical community and has led to fears that we may find ourselves again unable to combat such infections as tuberculosis, pneumonia and gonorrhoea³.

2. Of particular concern to public health are multidrug-resistant *Streptococcus pneumoniae* (a causative organism of pneumonia), methicillin-resistant *Staphylococcus aureus* (a common cause of nosocomial infection), which is threatening to become resistant to vancomycin as well, vancomycin-resistant *Enterococcus faecalis* and *E faecium*, multidrug-resistant *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae* (which causes gonorrhoea) and *Mycobacterium tuberculosis*, the TB bacterium^{2,4}. Resistant strains are transmitted rapidly from one country to another and also between animals and humans^{3,5}.

3. While the search for antimicrobials continues and has broadened to include natural substances produced by frogs and fish⁶, it is becoming increasingly unlikely that new antibiotics remain to be discovered which are more effective than those currently in use—nalidixic acid, the most recent new class, was introduced over 30 years ago. This has prompted researchers to investigate novel means of counteracting bacterial infection. One approach is to assign molecular “bodyguards” to existing antibiotics, as in the addition of clavulanic acid to amoxycillin in the drug Augmentin. This molecule binds irreversibly to the bacterial enzyme, β -lactamase, which destroys the active component in the penicillins. Scientists have also succeeded in designing molecules that bind to “pumps” in bacterial cell membranes which would normally be able to drive antibiotics straight out before they were able to damage cells⁷. Recent interest has focused on the development of oligosaccharide anti-infective agents—“decoy” oligosaccharides can block the binding of pathogens to host mucous membranes⁸. This mechanism is deemed unlikely to select for resistance as it not bacteriocidal and could be used to enhance the effects of classical antibiotics. A further line of research is concentrating on peptide antibiotics, especially the cationic peptides⁹. As these molecules rapidly disrupt bacterial cell membranes, again there is little likelihood of strains developing resistance.

4. The problem of increasing resistance to antimicrobial agents led to the convening of a WHO Scientific Working Group in Geneva in 1994¹⁰. Participants were asked to consider the questions of how to manage bacterial resistance and minimise its clinical and economic consequences; how to limit the emergence of resistance mechanisms and the spread of resistant bacteria; and how to improve surveillance systems and use them at the local, national and international levels¹¹. In brief, the following conclusions were made:

1. In order to monitor and provide surveillance of resistant organisms, to provide susceptibility data to clinicians and to detect significant resistance early, microbiology laboratories should be appropriately distributed geographically and their functions should be co-ordinated with those of reference laboratories.
2. Sociocultural attitudes and economic policies should be modified in order to limit bacterial resistance. The use of antibiotics in both humans and animals must be increasingly controlled and additional research on antibiotic resistance is needed*. Hospital infection control programmes are necessary to prevent infection, interrupt the spread of resistant bacteria, improve the efficacy of treatment and minimise the need for it.
3. Surveillance data must be accurate and networks between hospitals and cities extended. The database requires interpretation and integration with regard to ongoing activities in infection control and to programmes to guide antimicrobial selection¹².

SUBMISSION

5. The problem of increasing resistance to antimicrobial agents is of global importance. It is felt that a number of specific concerns should be submitted to the Committee.

6. It is apparent, and widely admitted^{2,3,9}, that the problem has arisen from the injudicious use of antibiotics, primarily from over-prescription:

- antibiotics are often prescribed for mild infections which could well be overcome by the body's own immune system, especially if the patient maintains a healthy lifestyle, or by the use of alternative remedies, depending on the ailment—topical antiseptics, oral rehydration therapy in cases of diarrhoea, etc.
- antibiotics may be prescribed for virus infection against which they are ineffective.
- in some countries, antibiotics are available over the counter and may be used inappropriately or a course of treatment not completed, leading to the selection of resistant strains.
- clinicians may prescribe before antibiotic susceptibility tests are carried out—although in the case of more serious infections it is obviously advisable to adopt this approach rather than allowing some time to elapse while swab cultures are made and sensitivity-tested, there is a danger that inappropriate antibiotics may be prescribed, exacerbating the problem of resistance.

7. In the early days of antibiotic use it was impossible to foresee the outcome of such practices but the problem of increasing resistance is not new and steps could have been taken to prevent it many years ago. There is no longer any excuse for mis-use of antibiotics; their availability without prescription must cease and clinicians must be educated to consider carefully the advisability of prescribing.

8. A further consideration, although not under the remit of this particular Committee, is the fact that prophylactic administration of antibiotics to animals has led not only to the emergence of resistant strains in these animals but to the ingestion by humans of meat containing low levels of antibiotics and the transfer between species of resistant strains of pathogens^{3,5}. It is inappropriate to enlarge on this point here but it must be mentioned and indeed the practice has been criticised by the WHO^{10,11,12}.

9. Good hygiene and application of basic infection control techniques not just in developing countries but in our own hospitals must be implemented. The role of hospitals in the dissemination of infections and the

*Emphasis could be given to sophisticated non-animal techniques.

emergence of multidrug-resistant strains of pathogens is well known. It is a deplorable fact too that in our inner cities some families are crowded together in insanitary and unhygienic conditions. Furthermore, in the much-criticised conditions of overcrowding associated with factory-farming, not only are animals predisposed by stress to succumb to infection but spread of infection will invariably be rapid.

10. It is also felt that concerns about the development of new drugs should be voiced. While most scientists and doctors agree that the likelihood of discovering new effective antibiotics is lessening and such discoveries may only provide a brief remission before new resistance strategies emerge, the pharmaceutical companies continue to screen for new antibiotics. Following development of new drugs, pre-clinical pharmacology involves the testing of the drugs in laboratory animals, initially rats and mice, to investigate the therapeutic effects and of course any possible toxic effects. Many scientists, doctors and members of the public consider the use of animals in product testing to be unscientific, unreliable and unethical. Species differences between humans and other animals plus inadequate human trials as a consequence of misleading test data have resulted in many instances of unsafe drugs being marketed to the public. For example, the heart drug *Eraldin*¹³ and the non-steroidal anti-inflammatory drug *Opren*¹⁴, used to treat arthritis, have now been withdrawn. Drug companies are therefore urged to consider using alternatives to animal testing.

11. When the time elapsed between Research & Development and a drug finally coming to market may be up to 15 years and the cost of the project may run into millions of pounds, any saving of time or money would be beneficial, if only to lower the final cost of the drug. Pharmacokinetic studies, ie studies which investigate the metabolism of the drug, are carried out at present in animals initially—obviously PK studies in human volunteers, part of Phase I trials, are of more value.

12. Any drug which is harmful to micro-organisms is likely to be harmful to higher organisms too and clinicians must decide whether any side effects outweigh the beneficial effects of the drug before prescribing—obviously a much easier decision to make them when an infection is life-threatening. Clinical trials in human volunteers have not however always provided enough information on harmful side effects and there have been cases where antibiotics have been withdrawn after having been in use for some time. While Adverse Events or Serious Adverse Events should be noted during clinical trials, Post Marketing Surveillance studies are carried out and doctors are encouraged to report any Adverse Drug Reactions once the drug is in widespread use, dangerous or even fatal side effects may only come to light after several years. Examples in the literature are too numerous to list here but one of the more widely-publicised examples is the antibiotic co-trimoxazole (*Septin*), reported to have caused a number of deaths^{15,16}—an outcome not predicted by toxicity tests on animals. Conversely a study which showed that hairless mice dosed with a quinolone antibiotic, lomefloxacin, and exposed to sunlight grew skin tumours more quickly than undosed controls was felt to be of no relevance to humans taking the drug¹⁷. Rather than withdraw the drug from the market, its manufacturers merely added a warning to avoid excessive sun. How relevant is animal testing therefore? In some cases it has failed to protect humans against harmful side effects—in others, it is ignored. A pharmaceuticals company has in fact been set up to test drugs exclusively on human tissue¹⁸. Its founders consider that the use of animals has become redundant in the light of advances in our knowledge of human genetics.

13. In conclusion, the recommendations of the WHO convention on resistance to antimicrobial agents are supported; some additional concerns relating to sanitation, hygiene and health education are voiced; and the opportunity has been taken to bring to the attention of the Committee some points involving the use of non-human animals in research and testing for human benefit and the need for better, more sophisticated research techniques.

Jan Creamer
Director

September 1997

REFERENCES

- 1 Finland M Changing patterns of resistance of certain common pathogenic bacteria to antimicrobial agents. *N Eng J Med* (1955) 252: 570-580.
- 2 Swartz MN. Use of antimicrobial agents and drug resistance. *New Eng J Med* (1997) 337: 491-492.
- 3 Pérez-Trallero E and Zigorraga C. Resistance to antimicrobial agents as a public health problem: importance of the use of antibiotics in animals. *Int J Antimicrob Agents* (1995) 6: 59-63.
- 4 Cormican MG and Jones RN. Emerging resistance to antimicrobial agents in Gram-positive bacteria—enterococci, staphylococci and nonpneumococcal streptococci. *Drugs* (1996) 51: 6-12.
- 5 Johnson AP. Veterinary use of antimicrobial agents and problems of resistance in human bacterial infections. *J Antimicrob Chemother* (1997) 39: 2285-286.
- 6 Valigra L. Engineering the future of antibiotics. *New Scientist* (1994) 142: 25-27.
- 7 Chin J. Resistance is useless. *New Scientist* (1996) 152: 32-35.
- 8 Zopf D and Roth S. Oligosaccharide anti-infective agents. *Lancet* (1996) 347: 1017-1021.
- 9 REW Hancock. Peptide antibiotics. *Lancet* (1997) 349: 418-422.

- 10 Bacterial resistance to antimicrobial agents. Editorial. *WHO Bulletin* (1996) 74: 335.
- 11 Acar JF, Kaplan EL and O'Brien TF. Monitoring and management of bacterial resistance to antimicrobial agents: a World Health Organisation Symposium—Geneva, Switzerland—29 November–2 December 1994—introduction. *Clin Inf Dis* (1997) 24: S1.
- 12 Acar JF, Kaplan EL and O'Brien TF. Monitoring and management of bacterial resistance to antimicrobial agents: a World Health Organisation Symposium—conclusion. *Clin Inf Dis* (1997) 24: S176.
- 13 Weatherall M. An end to the search for new drugs. *Nature* (1982) 296: 387-390.
- 14 *Scrip* (1988) 1284: 30.
- 15 *Scrip* (1994) 1996: 26.
- 16 *Scrip* (1994) 1902: 23.
- 17 *Scrip* (1993) 1807: 19.
- 18 Coughlan A. Pioneers cut out animal experiments. *New Scientist* (1996) 151: 4.

Memorandum by the Osborne Practice, Southsea

1. We feel that one of the major causes of antibiotic resistance is inappropriate prescribing of antibiotics by doctors. The most common circumstances in which doctors, especially general practitioners, prescribe antibiotics inappropriately is when they give them for viral illnesses. It is well known that antibiotics will have no effect on the cause of viral illness. This is elementary medical school education and yet doctors still persist in prescribing for this type of disease. Clearly, there must be reasons why well educated and competent professionals misuse antibiotics in this way. What are these reasons? We believe the reasons for this behaviour are as follows.

2. Over the past few years, doctors have been subjected to ever increasing numbers of complaints and litigation from patients. Doctors have responded to this situation by practising defensive medicine. This practice has adopted a very rigorous approach to antibiotic prescribing over the past few years and has had many complaints made against the practice by patients because we have not prescribed antibiotics to patients with viral infections such as sore throats and colds.

3. The evidence for not prescribing antibiotics in such situations is overwhelming and is also interesting to note that the paper in the current British Journal of General Practice describes a study in which it was found that an antibiotic called Doxycycline has no benefit over placebo in the treatment of sinusitis, a condition for which antibiotics are given, although perhaps without any rational foundation for this treatment. It has therefore been for the partners in this practice to defend themselves against complaints when patients have not received antibiotics when it is medically inappropriate for them to do so. However, complaints of this type cause a great deal of stress, time and resource consuming. The complaint often necessitates a number of letters going backwards and forwards between the Health Authority Complaints Commission, the patient and the practice. Often the practice's reply has to be vetted by the medical defence bodies. Expensive secretarial time is wasted in typing these letters and the time of the complaints staff at the Health Authority is wasted as well. The letters concerning the complaints are often followed up by a meeting between the patient, the doctor concerned and the conciliator. The time for the conciliator and doctor has to be paid for and the doctor's time has been taken away from his sick patients.

4. In addition to the resource implications, doctors take complaints very seriously and their emotional response to them is perhaps more averse than to some other groups receiving complaints. No doctor sets out with the intention of harming his patient and if something goes wrong and a complaint is made, the typical doctor will find this very stressful causing anxiety and sleepless nights etc. Even when the complaint can be easily rebutted, as in the case of not giving antibiotics for viral infections, there is still a considerable degree of stress involved in dealing with these complaints.

5. A second reason for doctors carrying out inappropriate prescribing for antibiotics is the time factor. It takes 30 seconds to write a prescription of antibiotics whereas it may take five minutes or more to educate the patients as to the reasons why they do not need antibiotics. This is not a feature of doctors laziness but of the pressures under which they find themselves having to work. Not only will the patient leave the surgery satisfied at having been given a prescription, but there is no adverse interaction with the patient. Patients often become angry, aggressive and sometimes even violent when they are refused the treatment they think they need. Carrying out a rigorous policy of only prescribing antibiotics where they are really indicated means the doctor being subjected to these type of pressures half a dozen to a dozen times a day which over the years becomes very wearing.

6. Doctors have become increasingly pressurised over the last six to seven years with more demands being made of them by patients, the government and society in general. Doctors are overloaded with work already and when numerous patients come in, often with colds and sore throats, often as "emergency" appointments, the pressure to move these patients through the surgery so that doctors can have time to deal with the patients who really need to see him increases. Unfortunately, this is a vicious downhill circle because the patient then comes back when they have their next cold expecting more antibiotics. However, as the doctors in this practice

can testify, it takes a tremendous effort, both emotionally and intellectually, to break out of this vicious cycle. Unfortunately, it is one that many and probably most GPs find themselves in.

7. Patients expectations have undergone a radical change in the past few years. Some of this has been encouraged by the Patient's Charter, but much of it is also a cultural change which is happening within our Society. Firstly, as mentioned in paragraph 2 above, patients who have been prescribed antibiotics for viral infections in the past, perhaps by doctors who have now been retired several years, still expect antibiotics for their colds, as it has already been outlined how difficult it is to break out of this pattern.

8. Another cultural change is that patients, particularly younger ones have a different perception on how their experience of life should be. They do not expect to suffer any pain, illness or ill fortune and if they do they expect these afflictions to be lifted from them instantly. For example, patients will come in to the doctor and say "my sore throat has just gone on and on and I can't stand it any more". When asked when it started they may say that it started last night or sometimes that it started that morning. Similarly, when other patients have been told they have a cold, they have been known to ask "Why me?" This question may be perfectly reasonable for a thirty five year old patient with leukaemia to ask, but it seems totally inappropriate in a young otherwise fit patient who has a cold. It shows a lack of appreciation that firstly, most people get three to four colds per year and secondly that we all have bad periods in our lives as well as good.

9. Patients tend to compare the NHS with commercial organisations, which often give extremely good standards of services. For example, patients will ask why surgeries cannot stay open all day, in the evenings and all day on Saturday and Sunday, like Sainsbury's. The answer to this is of course, that GPs are paid approximately £16 each year for patients they look after, whereas many people who shop at Sainsbury's spend £50-£100 on goods every week. Therefore, patients who are used to receiving good and instantaneous services in other areas expect the same service from their GP, who they expect to satisfy all their wants rather than their needs. Their wants often include antibiotics for viral infections. As described above, doctors will often give the antibiotics in these situations. With increasing pressure on doctors to increase standards and generally provide a better service this is one way in which superficially it can appear that the doctor is providing a better service to his patients. However, this unfortunately is contributing to the growing resistance of bacterial infections to antibiotics.

10. Doctors are selected by a variety of mechanisms to have a certain type of personality. They are generally compassionate people who go into medicine with a desire to help other people and alleviate their suffering. Their desire to help often make it psychologically very difficult to refuse requests made by their patients. There is a natural desire for a doctor to try and fulfil the patients' needs and wants. Unfortunately, this willingness to help spills over into areas where it is not appropriate, in this context; prescribing antibiotics for viral infection.

11. Another cultural change in society that makes it difficult for doctors to resist patients demands for inappropriate treatment is the decline in deference. Whilst this in itself is not necessarily a bad thing it means that doctors no longer command the respect or status within society that they use to. Therefore, when a doctor says that an antibiotic is not required for a cold or sore throat, the patient is very likely to challenge the doctor, and because of the fear of complaints and desire to give better service and so on, the doctor often finds it extremely difficult to resist the patients demands.

12. Another reason why doctors give antibiotics for viral infections is a purely pragmatic one. If the patient is thwarted in his desire to get antibiotics they will often threaten to call out the doctor at night and at weekends. It takes a very strong personality to resist the demand to give a prescription for antibiotics when you know refusal will result in you being called out of bed at 3 o'clock in the morning to go through the same process.

13. The next factor involved in reasons why doctors find it difficult to make changes towards better antibiotic prescribing is poor morale. Morale amongst doctors generally and in general practice in particular is extremely low at the moment. Since the changes introduced in 1991, morale in general practice has plummeted. Increasing complaints, litigation and workload combined with ever increasing demands to increase clinical performance are taking their toll of doctors. Added to that is the ever increasing managerial and administrative tasks being laid on doctors shoulders, which all lower morale. A bureaucratic and often low standard system of management compounds the problem. Often, ill thought out changes without sufficient consultation with all the health professionals involved are imposed in various sectors of the NHS. Because they are implemented hurriedly and without due planning and piloting the new policies often prove unworkable, yet the pressure is on GPs to implement these policies. Often these policies are of no benefit to the patients at all and sometimes are even counter productive, yet the doctors are still forced by the civil servants and managers to implement these policies, further destroying morale.

14. Financial pressures are a major contributing factor to the poor morale amongst GPs at present. Our salaries have decreased by 50 per cent in real terms. Further more practices are having their arms twisted by managers to buy expensive computers, often costing the practice £20,000-£30,000 when all the benefit from these computers appears to be for the NHS administration and no obvious benefit for the patients or doctors. Pressures of doctors being under-funded (most accountants estimate by an average of £5,000-£6,000 a year) plus all sorts of hidden pay cuts in reduced reimbursement for expenses such as staff costs and the hidden costs that have come about due to the deterioration of the NHS over the last few years are depressing to most doctors. These sort of costs include making several phone calls to a hospital department, having been cut off

several times by a hospital telephonist who herself is operating under such pressure that they are no longer able to do their job effectively and efficiently. Most GPs could identify dozens if not hundreds of hidden financial time and emotional costs that have become an increasing burden recently.

15. Drug companies aggressively market new antibiotics. Doctors are put under pressure by advertising sales reps to prescribe new antibiotics, the main pressure being that these are better, more effective, have less side effects etc etc. Most doctors are sensible enough to resist these pressures. However, there are a minority who are gullible enough to be taken in by the drug companies claims that these drugs are more effective and will not be subject to resistance in the future. Fortunately, I have seen treatment prescriptions from doctors in other practices who have seen our patients "out of hours" where there has been a diagnosis on the card of URTI (upper respiratory tract infection = cold) and a prescription for Ciprofloxacin has been given. Firstly, it is totally inappropriate to give an antibiotic of any sort in this situation and it is even worse to give a powerful fourth generation antibiotic such as Ciprofloxacin. This serves no benefit to the patient and merely increases the chance of resistance to this new antibiotic being produced.

16. The remedies to these problems that the Government and NHS might implement:

- (a) To educate the public. The public need to understand that there are certain illnesses which are minor and self limiting. Most of these illnesses are viral and therefore do not need antibiotics. In general, it is not necessary to see the doctor for these illnesses and that they can be treated quite adequately with advice from the chemist. The public needs explanations that unnecessary antibiotics will bring about antibiotic resistance and with all the subsequent consequent risks to the health of the country in future. It is even possible that we are entering a "post antibiotic age" and the public need information to help them understand the consequences of this and that by demanding antibiotics when they are not appropriate they are speeding our entry into the new age.
- (b) It might be possible for a technical and medical committee to make a clear statement that doctors should not prescribe antibiotics for viral infections such as colds. This would help strengthen a doctors hand when trying to resist pressures from patients. It would also be helpful if advice could be given to the complaints departments at the various health authorities that complaints of this nature (as opposed to complaints concerning other matters) should be stopped by the complaints officer at a very early stage. It should be made very clear to the patient that the doctor is correct not to prescribe antibiotics for a viral illness. This is probably the most important factor in the future. We know from discussions from our colleagues that the threat of complaints is the single largest factor which inhibits change in this area.
- (c) Improve doctors education. Many medical students, when they enter medical school, have not taken any biological sciences at A-Level and there is no basic biology or evolutionary theory taught at medical school. Therefore, many doctors do not have a good grasp of evolution and the evolutionary reasons for bacteria developing resistance to antibiotics. This could be improved by teaching evolutionary medicine at both under-graduate and post-graduate levels. Dr Bruce Charlton at Newcastle University is at present trying to establish a group to implement the teaching of evolutionary medicine at medical schools. I think he should be encouraged to achieve his aims.
- (d) Improve morale. Doctors morale and especially that of GPs is at rock bottom at present. The thought of making yet another change in their mode of practice is more than many (probably a majority) GPs can contemplate at a time when they feel increasingly stressed, pressurised, insecure and depressed. They feel undervalued and under paid. In these circumstances, most GPs feel that they are struggling to survive and there is a great deal of apathy concerning change of any sort, even when it is so clearly necessary.

SUMMARY

There are a number of factors which cause doctors to prescribe antibiotics inappropriately. Most important of these are probably complaints and litigation from the patients. However changes in culture and society are also important. Education of doctors is another factor although, we believe, less important than some of the other factors. The low morale and depression in doctors is a particularly relevant factor in opposing change.

Possible remedies including educating the public, support for the doctors from government and scientific and medical committees. Improved education for medical students and trainee doctors would help in the area of evolutionary medicine and how resistance to antibiotics arises. Improving morale amongst doctors and make them feel valued public servants is an especially important factor. Deflecting complaints about not prescribing antibiotics for colds would be very helpful.

Dr B D Mitchell
Dr J P D Price
Dr M Robinson
Dr L Russell

Memorandum by Dr Laura J V Piddock, University of Birmingham**SUMMARY**

- Antibiotic resistance has been my principal research interest for 15 years. My group has concentrated upon researching the mechanisms of antibiotic action and bacterial resistance. Since 1987 I have headed a team of 6-10 people at the Department of Infection, University of Birmingham (Head of Department: Professor A. M. Geddes). I have published 60 (plus one in press and three submitted) original research articles, 15 review articles and 12 letters to Editor's in international peer reviewed journals, and made 62 presentations of original research at international conferences. I have written 2 chapters in academic books.
- Current research focuses upon resistance in the enteric bacteria salmonella, *Campylobacter* and *Escherichia coli* and those that cause infections of the respiratory tract, including tuberculosis. These pathogens cause two of the most important infections in the world, giving rise to great morbidity and mortality.
- I am an active investigator into the role of antibiotic use in animals, effect upon the reservoir of resistant bacteria that infect man and human health implications. In this role I was an invited participant at the recent World Health Organisation meeting in Berlin in October 1997.
- Attached is a summary of research from my team on three topics that I deem of interest to the Committee: antibiotic-resistance in foodborne bacteria, antibiotic-resistance in bacteria causing respiratory tract infections and how antibiotic-resistant bacteria can emerge.

1. ANTIBIOTIC-RESISTANCE IN FOODBORNE BACTERIA

- Since 1987 I have researched the mechanisms of antibiotic resistance in foodborne bacteria including *Salmonella*, *Campylobacter*, and *E.coli*. I have collaborated with a variety of groups world-wide and include Public Health Laboratories, Ministry of Agriculture Fisheries and the Central Veterinary Laboratory.
- Due to the research output of my team, I have been invited and presented as an expert adviser:
 1. In 1994 to the Food and Drugs Administration (FDA; USA) during their consideration of licensing of fluoroquinolones for use in food animals.
 2. In 1995 to the UK Ministry of Agriculture, Fisheries and Food (MAFF) when the use and licensing of antibiotics in general for food animals was reviewed.
 3. August 1996-present, member of the Working Party of the Department of Health Advisory Committee for the Microbiology Safety of Food: role of antibiotic use in animals and implications in human health. We have met every four weeks, reviewed a large amount of literature, and taken presentations from all interested parties within this field. I have also provided a detailed report on mechanisms of antibiotic resistance and antibiotic resistance gene transfer within bacteria, with particular relevance to foodborne pathogens. This working party is nearing conclusion and will be making formal recommendations to government early in 1998.
 4. August 1997-present I am co-contractor with Dr David Taylor from Glasgow Veterinary School of a MAFF contract to undertake the largest ever review of published literature on antibiotic resistance in foodborne bacteria. As part of this I organised an International Workshop in Birmingham on Friday 31st October.
 5. October 1997 temporary adviser to the World Health Organisation (WHO) on the Medical Impact of Antibiotic use in food animals. I submitted and orally presented a working paper at a five day workshop in Berlin at which there were 40 invited experts from around the world plus 30 observers from Federal Agencies and Pharmaceutical companies. 20th October 1997, the World Health Organisation issued a press release and their formal recommendations will be available during November 1997.
 6. February 1998 I will attend a joint WHO/FDA and CDC meeting in Washington, USA on the Licensing and the use of fluoroquinolone antibiotics in food animals.

Invited articles on this issue:

Piddock, LJV. Use of fluoroquinolones in animals. *ASM News*. 61: 101

Piddock, LJV. (1996). Does the use of antimicrobial agents in veterinary medicine and animal husbandry select antibiotic resistant bacteria that infect man and compromise antimicrobial chemotherapy? *Journal of Antimicrobial Chemotherapy* 38: 1-3

PUBLISHED RESEARCH WORKS INCLUDE

1. *Mechanism of fluoroquinolone, and multiple drug resistance, -resistance in Salmonella typhimurium isolated from man*

Detailed investigations have been performed on the mechanisms of antibiotic resistance in isolates of *S. typhimurium* from two patients from Monsall Hospital in Manchester from which ciprofloxacin resistant strains emerged during therapy. Essentially the data has shown that *S. typhimurium* can contain mutations in the genes that encode the target proteins for fluoroquinolones, but also exposure to fluoroquinolones can lead to multiple drug resistance encoded by one locus. In addition we have shown that similar mutations occur in *S. typhi* from patients in Viet Nam.

Piddock LJV, Whale K, & Wise R (1990) Quinolone resistance in salmonella: clinical experience. *Lancet*, 335 June 16: 1459

Piddock LJV (1990) Ciprofloxacin resistance in salmonella serotypes. *Journal of Antimicrobial Chemotherapy*, 26: 853-863

Piddock LJV, Griggs DJ, Hall MC, & Jin YF (1993) Ciprofloxacin-resistance in Clinical isolates of *Salmonella typhimurium* obtained from two patients. *Antimicrobial Agents and Chemotherapy*, 37: 662-666

Gensberg, K, Jin, YF and Piddock, LJV 1995. A novel *gyrB* mutation in a fluoroquinolone-resistance clinical isolate of *Salmonella typhimurium*. *FEMS Microbiology Letters* 132: 57-60

Griggs, DJ, Gensberg, K & Piddock, LJV (1996). Mutations in the *gyrA* gene of quinolone-resistant salmonella serotypes isolated from man and animals. *Antimicrobial Agents and Chemotherapy*, 40: 1009-1013.

Wain, J, MJ Everett, NT Hoa, NJ White, & Piddock, LJV (1997). Mutations in *gyrA* of *Salmonella typhi* isolates from Southern Viet Nam. *Clinical Infectious Diseases* (In Press, December).

2. *Mechanism of fluoroquinolone resistance in salmonella isolated from animals (collaboration with Dr Clifford Wray, Central Veterinary Laboratory)*

Although nalidixic acid-resistant *Salmonella* have been isolated from animals, these isolates are apparently still susceptible to clinically achievable concentrations of fluoroquinolones in serum of man, and would be considered susceptible to the internationally recommended breakpoint concentrations of various fluorquinolones (between 1 and 4 µg/ml). However, the work on *S. typhimurium* and *S. typhi* from man has shown that the recommended breakpoint concentrations of fluoroquinolones may not be useful for indicating therapy failures for these agents in man with complicated or systemic salmonellosis. So, although the isolates for animals appear as if they would be treatable if they caused an infection in man this may not be the case. We have suggested that the recommended break point concentration used for salmonella should be reduced. If this were the case then many of the isolates from animals would be considered clinically resistant.

Piddock LJV, Wray C, McClaren I, & Wise R (1990) Quinolone resistance in *Salmonella spp*: veterinary pointers. *Lancet*, 336: 125

Wray C, McClaren I, Wise R, & Piddock LJV (1990) Nalidixic acid-resistant salmonellae. *The Veterinary Record*, May 12: 489

Griggs, DJ, Hall, MC, Jin, YF & Piddock, LJV (1994) Quinolone-resistance in veterinary isolates of *salmonella*. *Journal of Antimicrobial Chemotherapy*, 33: 1173-89

Piddock, LJV, V.Ricci, I McLaren, & DJ Griggs. Role of mutation in the *gyrA* and *parC* genes of 196 nalidixic acid-resistant salmonella serotypes isolated from animals. (Submitted to *Journal of Antimicrobial Chemotherapy*, September 24th)

3. *Mechanism of fluoroquinolone resistance in Escherichia coli isolated from animals (isolates from Dr Clifford Wray, Central Veterinary Laboratory, Spain and Argentina)*

Eight veterinary isolates from CVL, and 28 human isolates of *E. coli* from Argentina and Spain, required 2-> 128 µg/ml ciprofloxacin for inhibition. Detailed analyses demonstrated multiple mutations in the genes encoding the fluoroquinolone target proteins, *gyrA*, *gyrB* and *parC*, plus changes in the outer membrane protein and lipopolysaccharide profiles of all isolates. Previously these have been associated with decreased permeability of the bacterium to antibiotics and to cause low level multi-drug resistance. For 19 isolates significantly lower concentrations of ciprofloxacin were accumulated, attributed to be due to active efflux of the drug from the bacteria. These data indicate that high-level fluoroquinolone resistance in *E. coli* involves the acquisition of mutations at multiple chromosomal loci. Many of the human isolates came from patients with a UTI, which were untreatable with a fluoroquinolone. It is interesting to note that the isolates from poultry possessed fewer mutations than those from man, and in my opinion the acquisition of multiple mutations culminating in high level resistance is due to the repeated exposure of the organism to antibiotic, allowing the step-wise accumulation of mutations. The primary exposure is likely to be in an animal due to the veterinary use of fluoroquinolones, these bacteria are then ingested and become part of the commensal flora, and in those susceptible to UTI, enter the urinary tract and cause infection. I am currently collaborating

with Dr. David White from the USA on the mechanism of multiple antibiotic resistance in avian *E. coli* isolated after fluoroquinolone exposure.

Everett, MJ, Jin, YF, Ricci, V & Piddock, LJ (1996). Contribution of Individual mechanisms to fluoroquinolone resistance in 36 *Escherichia coli* isolated from humans and animals. *Antimicrobial Agents and Chemotherapy*, 40: 2380-2386

4. Mechanism of fluoroquinolone and multi-drug resistance in *Campylobacter* from man and from animals (collaboration with Dr Nick Gaunt from Plymouth Public Health Laboratory)

From the end of April 1991 to December 1994, 91/2209 (4.1%) ciprofloxacin-resistant (CIP^R) *Campylobacter* were isolated at Plymouth PHL. Their susceptibility to ciprofloxacin ranged from 8->128 µg/ml and there was an association with resistance to tetracycline, but not kanamycin or erythromycin. A case-control study demonstrated that the association of foreign travel and CIP^R *Campylobacter* enteritis was highly significant. However, foreign travel accounted for only 39 per cent of cases, the remainder being acquired in the UK. Since chicken is the most frequent food source of *Campylobacter*, 64 UK-bred and 50 non-UK bred chickens were examined for *Campylobacter*: 27 per cent of the isolates from the imported birds were CIP^R, whereas only one UK bird contained a resistant isolate, suggesting that imported poultry may be the origin of UK-acquired CIP^R *Campylobacter* enteritis. All isolates of CIP^R *Campylobacter* were subjected to detailed analysis for the mechanism of resistance: most isolates, including those from poultry, contained identical point mutations in the gene encoding the target of fluoroquinolones, *gyrA*. The increasing numbers of CIP^R *Campylobacter* in countries such as The Netherlands has been attributed to the veterinary use of quinolones, notably enrofloxacin, suggesting that it provides a selective pressure for emergence of resistance to ciprofloxacin amongst human isolates. Since enrofloxacin was licensed for use in broiler flocks in the UK, we have continued to monitor the prevalence, and mechanism, of resistance of *Campylobacter* to quinolones from patient isolates at Plymouth.

While it is not usual, or recommended, to treat enteric infections with antibiotics there is an increasing use of these agents by General Practitioners because there is a clear perception of reduction of duration of symptoms. Although this has not been associated with any reduction of time to eradicate the bacteria, the widespread advertising of this particular use of fluoroquinolone both in the medical literature and in the general media including daytime television, has meant that there has been much pressure on GPs to prescribe these agents. Therefore, as the *Campylobacter* are resistant to these agents there is a very real likelihood that patients will not respond to therapy.

As with the salmonella and *E. coli* many of the fluoroquinolone-resistant *Campylobacter* are multiply drug resistant. In my opinion there is the very real possibility that fluoroquinolones select for multi-drug resistance due to mutation at one genetic locus.

Piddock, LJ., Williams, T.J. & N. Gaunt (1993) Ciprofloxacin-resistant *Campylobacter* species from man and foodstuffs in the United Kingdom. *Recent Advances in Chemotherapy* 261-2

Gaunt, PN. & Piddock, LJ. (1996) Ciprofloxacin resistant *Campylobacter* in humans: an epidemiological and laboratory study. *Journal of Antimicrobial Chemotherapy* 37: 747-757

Piddock, LJ. Quinolone and *Campylobacter* resistance. (1995) *Journal of Antimicrobial Chemotherapy* 36: 891-898

CONCLUDING REMARKS

The research from my laboratory has clearly shown that contrary to the accepted wisdom in the late 1980s that fluoroquinolone-resistance would not occur in bacteria considered to be exquisitely susceptible to these agents, it has emerged in clinically significant enteric pathogens. While some of the strains have undoubtedly emerged due to the use of these agents in man, there is convincing data to support the hypothesis that the use of fluoroquinolones in veterinary medicine is increasing the reservoir of antibiotic-resistant strains. These can enter the food chain, and in susceptible hosts cause an infection for which a fluoroquinolone is often the first choice for therapy. There is now considerable evidence, particularly that from the Laboratory of Enteric Pathogens, Public Health Laboratory Service, that fluoroquinolone-resistant salmonella (including DT104) are increasing in the human population, and this has also been attributed to the use of fluoroquinolones in animals. Work in my laboratory on the mechanism(s) of resistance has shown that while many of these enteric bacteria are only resistant to fluoroquinolones, and so another antibiotic can be used to treat the patient if necessary, a significant number of the resistant strains are also multiply antibiotic resistant which is extremely worrying as use of one agent may be selecting such strains, thereby vastly reducing the therapeutic options should antimicrobial chemotherapy be required.

2. ANTIBIOTIC-RESISTANCE IN BACTERIA GIVING RISE TO RESPIRATORY TRACT INFECTIONS

1. Mechanism of multiple antibiotic resistance in post-enoxacin therapy isolate of *Pseudomonas aeruginosa*

P.aeruginosa usually colonises individuals whose immune status is compromised by the nature of their disease or by prolonged chemotherapy. In the past, the vast majority of isolates of *P.aeruginosa* were generally sensitive to most antibiotics, but with increasing use of these agents to treat infections, particular infections of the respiratory tract a predominant percentage of more resistant strains have been recognised. During therapy for pseudomonal infection in a patient with Chronic Obstructive Airways Disease, a clinical isolate of *P.aeruginosa* (G48), became resistant to the fluoroquinolone enoxacin, giving rise to the post-therapy isolate, G49. As has been found with other fluoroquinolone-resistant bacteria, there was a mutation in the gene encoding the target protein. However, genetic experiments to reverse this effect showed that this mutation was only partly responsible for the resistance. G49 is also resistant to several antibiotics, and does not express a major outer membrane protein associated with cell permeability. Recent data suggests that G49 is multiply antibiotic resistant due to efflux from the cell of several antibiotics.

Piddock LJ, Wijnands WJA, & Wise R. (1987) Quinolone/Ureidopenicillin cross-resistance. *Lancet*, Oct 17:907 (Letters to Editor)

Piddock LJ, Hall MC, Bellido F, Bains M, & Hancock REW. (1992). A Pleiotropic, Post-Therapy Enoxacin-resistant Mutant of *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy* 36, 1057-1061

Pumbwe, L, Everett, M.J., Hancock R.E.W., & Piddock, LJ. (1996). Role of *gyrA* mutation and loss of OprF in the multiple antibiotic resistance (MAR) phenotype of *Pseudomonas aeruginosa* G49. *FEMS Microbiology Letters* 143: 25-28

2. Mechanism of fluoroquinolone resistance in *Streptococcus pneumoniae*

Infections due to *S.pneumoniae* continue to be a significant cause of morbidity and mortality. Traditionally, penicillin has been considered the drug of choice for the treatment of pneumococcal infections. Penicillin-resistant pneumococci were first reported in 1967 and have continued to be isolated such that in some countries penicillins are no longer useful in the treatment of infections caused by this species. As fluoroquinolones have a broad spectrum of activity, and concentrate within the bronchial mucosa increasingly these agents are used to treat respiratory tract infections. Clinical failure of ciprofloxacin and ofloxacin has been reported for pneumococci in several countries including the United Kingdom. In my laboratory spontaneous quinolone-resistant mutants of *S.pneumoniae* were shown to arise after one exposure to ciprofloxacin in agar. We further characterised the mechanism of resistance in such mutants. In parallel studies elsewhere with clinical isolates similar mechanisms of resistance were demonstrated.

LJ Piddock & R Wise. (1988). The selection and frequency of streptococci with decreased susceptibility to ofloxacin compared with other quinolones. *Journal of Antimicrobial Chemotherapy* 22 Suppl. C: 45-51

Piddock LJ & Jin Y-F. (1992). Selection of spontaneous quinolone-resistant mutants of *Haemophilus influenzae* and *Streptococcus pneumoniae*. *Journal of Antimicrobial Chemotherapy* 30: 109-10.

Piddock, LJ, Jin Y-F. & Everett, M.J. (1997). Non-*gyrA* mediated ciprofloxacin-resistance in laboratory mutants of *Streptococcus pneumoniae*. *Journal of Antimicrobial Chemotherapy* 39: 609-616

3. Mechanism of fluoroquinolone resistance and antibiotic accumulation by *Mycobacterium tuberculosis*

Although several hundred antimicrobial agents are currently available world-wide, very few are effective against *M. tuberculosis* and even fewer are effective against "atypical mycobacteria", such as *Mycobacterium avium* complex. It has been widely proposed that the mycobacterial cell wall has low permeability and that this reduced permeability plays a major role in the intrinsic resistance of mycobacteria to most antibiotics. However, little study of the accumulation/transport of anti-tuberculous agents by mycobacteria, or the role permeability plays in mycobacterial drug resistance, has been performed. Since 1994, in order to gain further insight into mechanisms of fluoroquinolone accumulation by mycobacteria the accumulation of norfloxacin and rifampicin by *M.aurum*, *M.smegmatis* and *Mycobacterium tuberculosis* has been investigated. This work is now nearing completion and three papers have been submitted for publication. In parallel, due to the expertise in my laboratory on mechanisms of fluoroquinolone-resistance, and as part of a collaboration with researchers from Hong Kong, the role of mutation in *gyrA* was determined with clinical isolates of *Mycobacterium tuberculosis*.

Williams, KJ, Chan, R. & Piddock, LJ. (1996). Characterisation of mutations in *gyrA* of ofloxacin-resistant clinical isolates of *Mycobacterium tuberculosis* from Hong Kong. *Journal of Antimicrobial Chemotherapy* 37: 1032-1034

CONCLUDING REMARKS

Treatment of respiratory tract infections with antibiotics continues to increase, often due to the lifestyles many find themselves living and working in the 1990s. An understanding of the mechanisms of resistance of antibiotic accumulation into the bacterium will give some insight into the development of new agents.

3. ADAPTIVE MUTAGENESIS TO GIVE ANTIBIOTIC RESISTANCE IN *ESCHERICHIA COLI* (COLLABORATION WITH B.G. HALL, UNIVERSITY OF ROCHESTER, USA)

Experiments by Luria & Delbruck in 1943 and later others, led to the dogma that all mutations occur randomly without respect to utility. In 1988, Cairns *et al.*, showed that under prolonged non-lethal stresses such as carbon starvation, mutants arose in the non- or slowly growing population that permitted utilisation of an alternative carbon source not used by the parent strain. A key, and surprising, observation was that the mutants did not arise in the absence of the alternative source, ie when they were not useful. Subsequent experiments by Hall and others have confirmed that "adaptive mutations" occur in many genes in both procaryotic and eucaryotic organisms. The key feature of the phenomenon of "adaptive" mutagenesis is that it is time-dependent and apparently allows mutations to occur much more often when they are useful than when they are neutral. In March 1995 I started a collaboration with Prof. Hall to investigate the hypothesis that adaptive mutagenesis could allow antibiotic-resistant organisms to arise. Late arising antibiotic-resistant mutants were obtained with two chemically unrelated antibiotics in both laboratories. Approximately 50 per cent of the 67 mutants investigated were multiply antibiotic resistant. If exposure to an antibiotic allows the survival of multiply antibiotic resistant mutants, treatment of an infection caused by *E. coli* with one antibiotic will select resistance to other agents including fluoroquinolones, tetracycline, chloramphenicol, trimethoprim and some β -lactams. If exposure to antibiotics not only selects resistant strains emerging randomly, but also "induces" resistance then this could explain why certain bacteria and/or antibiotics have a very high frequency of emergence of clinical resistance. The selection of adaptive mutants with clinically low level resistance, will contribute to the pool of organisms that may give rise to mutants with clinically relevant levels of resistance. Current work is pending funding (application submitted to The Wellcome Trust) and if funded will focus upon the role of specific chromosomal genes giving rise to adaptive mutants. I would also like to see whether this phenomenon is specific to *E. coli* or is ubiquitous to other human pathogens (as is suggestive by work on the phenomenon of adaptive mutagenesis).

Riesenfeld, C., Everett, MJ., LJV Piddock & Hall, B.G. Adaptive mutations produce resistance to ciprofloxacin. *Antimicrobial Agents and Chemotherapy* 41: 2059-2060

Memorandum by the Research Council for Complementary Medicine

COMPLEMENTARY MEDICINE IN THE TREATMENT OF INFECTION

BACKGROUND

One response to the rise in antibiotic resistance is to examine methods of treating and preventing infectious disease which do not depend on the use of antibiotics. Such methods can be found in the activities of practitioners of complementary medicine (CM) who use therapies such as acupuncture, herbalism or chiropractic. This brief will discuss the evidence that CM interventions might form part of the response or rising resistance to antibiotics. The evidence will be examined in the light of three claims.

- 1) Infectious disease may be treated or prevented by interventions which improve immune function.
- 2) Infectious organisms can be killed by using plant material containing a large number of chemical components.
- 2) CM interventions may provide an appropriate substitute for antibiotics where antibiotic use is not essential.

As a general narrative overview, the main aim of the brief is to guide further research. Accordingly, not all evidence is presented. For example, some trials which failed to find differences between experimental and control treatment are not mentioned here because, partly as a result of their negative findings, they do not constitute fruitful areas for future research. Emphasis is placed instead on what seem the most promising areas for investigation. Moreover, a lack of evidence in favour of a particular intervention should not be interpreted as evidence that the intervention is not of benefit. CM is largely unresearched. What research has been conducted has often been a function of individual workers' particular interests, rather than being due to the importance of the question being asked.

1. Can CM interventions improve immune function?

1.1 Herbal Medicine. There is good evidence that preparations containing extracts of plants from the *Echinacea* family can improve immune status in healthy volunteers (see for example, Bauer *et al.*¹) There is also evidence that such preparations can be of clinical benefit. In two separate randomised, double-blind studies, Bräunig *et al* found that both high dose *Echinacea purpurea* and *Echinacea pallida* reduced symptoms

in upper respiratory tract infections^{2,3}. Prophylactic use of *Echinacea purpurea* has also been shown to reduce the risk (albeit slightly) of such infections⁴. Melchart et al.⁵ report that there are a further 15 randomised trials of preparations containing *Echinacea* for the treatment or prevention of infection, 13 of which have positive results.

1.2 Relaxation techniques. It is hypothesised that, because anxiety and stress can reduce immune function, therapies designed to induce relaxation may improve immune response. There have been a considerable number of trials investigating changes in immune status (by measuring, for example, salivary IgA) in healthy volunteers following training in relaxation, self-hypnosis or meditation techniques⁶⁻¹⁶ or after massage^{6, 18}. Most, though not all, show improvements in immune function. A smaller number of trials¹⁹⁻²¹ have examined patient populations. These have broadly similar findings. However, no trial has used a clinical outcome measure (eg number of infections, duration of illness) and the clinical significance of the reported changes in immune parameters remains unknown. As such, there is little evidence that more widespread uptake of relaxation techniques would lead to any major decrease in antibiotic use.

1.3 Nutritional interventions. Vitamin C has been widely promoted as an effective method of preventing respiratory infections, but its use remains controversial. The current scientific consensus is that it does not have a large, consistent or generally applicable effect²². However, it may have a role in particular sub-groups, for example, those with low intake (such as male school children)²³ or those under heavy physical stress²⁴. Furthermore, there is good evidence that vitamin C may be effective treatment for the symptoms of the common cold²⁵, particular for people with severe symptoms. For instance, Hunt et al randomised 57 elderly patients admitted to hospital with acute respiratory infections to vitamin C or placebo²⁶. Patients receiving placebo had a significantly poorer symptomatic response.

Zinc has also been promoted as a treatment for the common cold. There is now some evidence to support this claim. In one randomised, double-blind trial, zinc lozenges were found to reduce the duration of cold symptoms²⁷.

1.4 Homoeopathy. Although one study has found that use of homoeopathic medicine prophylactically does not reduce the incidence of upper respiratory tract infection²⁸ there is good evidence that one particular remedy, known as *Oscillocochinum*, can be of benefit for 'flu and 'flu-like symptoms²⁹. Nearly 500 patients were randomised to homoeopathy or placebo on a double-blind basis. The proportion of cases who recovered within 48 hours of treatment (defined as complete resolution of pre-defined symptoms and a rectal temperature < 37.5 degrees) was greater in the homoeopathy group than in the placebo group (17.1 per cent against 10.3 per cent, $p = 0.03$).

Homoeopaths do not normally treat infections using a single standard remedy, rather than give different remedies to different individuals depending on the results of a homoeopathic interview. A trial which studied homoeopathy as it is usually practised randomised 175 children with recurrent upper respiratory tract infections³⁰ to homoeopathy or placebo. Though differences in symptom scores were only of borderline statistical significance, what is of particular interest is that antibiotic use fell greatly in both groups, but slightly more in those receiving homoeopathy. Though about 85 per cent of children entering the trial had taken antibiotics in the year before the trial started, only 35 per cent of children taking homoeopathy did so in the one year of the trial.

2. Can plant material containing a large number of chemical components be of benefit for infection?

2.1 Background. It is well understood that plants contain antimicrobial substances, after all, plants need to avoid attack from bacteria, fungi and so on. A traditional approach to drug development has been to isolate individual compounds from plant material, screen them from antimicrobial activity and then synthesise promising compounds in the laboratory. Another approach would be to note that an extract from a plant contains a large number of substances, that more than one of these may have antimicrobial effects and that therapeutic effects may result from complex interactions between different components. For example, citral and geraniol are common plant terpenes which have been shown to have activity against both *Staphylococcus* and *Enterobacter*³¹. Lemongrass oil contains both compounds, as well as about 15 other components³². It is plausible that antibiotic resistance is less likely to result from use of drugs containing many compounds than from those using only a single type of molecule. Though this possibility has yet to be researched systematically, it is of note that bacterial resistance to single antibiotic agents has become common after only half a century of use whereas plants retain good immunity to bacterial infection despite depending on antibiotic agents which have been ubiquitous in the environment for thousands if not millions of years. It is also possible that herbal preparations may be effective against antibiotic resistant bacteria. For example, essential oil of tea tree has been found to have in-vitro activity against both methicillin and mupirocin-resistant *Staphylococcus aureus*³³.

2.2 Clinical research. With the exception of antimalarials, which fall somewhat outside the scope of this brief, there have unfortunately been only a small number of trials which have examined the use of plant drugs for infectious disease. Ferley et al³⁴ failed to show an effect of a plant remedy known as "Gouttes aux Essences" (containing peppermint, lavender, cinnamon, thyme and clove oil) in 182 elderly subjects with chronic bronchitis randomised to the drug or placebo. On the other hand, there is evidence from three randomised trials that topical application of tea tree oil is of benefit for skin infections including acne³⁵, tinea

pedis³⁶ and onychomycosis³⁷. In the first of these, 124 patients with acne were randomised to benzoyl peroxide or tea-tree oil. Outcome was assessed by blinded lesion counts. No difference in outcome was found between the two treatments, though patients using tea tree experienced fewer adverse effects. The trials finding tea-tree of benefit for acne and onychomycosis are of particular interest for this brief, as both conditions are sometimes treated with oral antibiotics. A recent, well-publicised trial of cranberry juice for cystitis, published in the Journal of the American Medical Association³⁸, is of interest for the same reason.

3. CM interventions may provide an appropriate substitute for antibiotics where antibiotic use is not essential

There is evidence that prescription of antibiotics depends on psychosocial features of the consultation as well as on clinical considerations. For example, GPs are consulted to “legitimate” a patient’s illness; antibiotics may be prescribed as part of the legitimisation process³⁹. Alternatively, a prescription may be written as a socially acceptable method of ending a consultation⁴⁰. It is plausible that prescription of herbal, homoeopathic or nutritional remedies—particularly those for which there is evidence of benefit such as *Echinacea*, *Oscillocochinum* or vitamin C—could replace prescribing of antibiotics. Prescription would retain its social function without contributing to any rise in antibiotic resistance. However, there is currently very little evidence that use of antibiotics could be lowered without leading to poorer clinical course by use of such a strategy. One survey of homoeopathic physicians did find that they gave 12 per cent fewer prescriptions than average⁴¹. However, this could result from differences in case mix rather than the use of homoeopathy.

RECOMMENDATIONS

1. Further trials of *Echinacea* products in general practice are warranted. Patient and practitioner acceptability should be assessed and antibiotic use should be an outcome.
2. The long-term safety of *Echinacea* products needs to be assessed.
3. Research on relaxation endpoints should include clinical endpoints rather than just immune function. However, research in this area should probably not be prioritised.
4. Research needs to identify which, if any, sub-groups are likely to benefit from prophylactic use of vitamin C.
5. The trial on zinc for the common cold needs to be replicated.
6. Homoeopathic *Oscillocochinum* appears to be an effective remedy for ‘flu like symptoms. However, given the low plausibility that homoeopathic medicines have different clinical effects from placebo, further trials are required.
7. Trials comparing homoeopathic treatment to standard GP care in the treatment of recurrent infection are warranted. Antibiotic use should be an outcome.
8. Research should examine the acceptability to patients and practitioners of prescribing herbal, homoeopathic or nutritional supplements in place of antibiotics where antibiotic use is not essential. Antibiotic prescribing should be an outcome as well as clinical course.
9. Development of antibiotic treatments from plant material should involve both isolation of individual plant compounds (the current approach) and research on whole plant extracts.
10. Further trials of herbal antibiotics, particularly essential oil of tea tree, are warranted.
11. Research on CM interventions such as herbal antibiotics is currently at a commercial disadvantage because products cannot usually be patented. Government funding of such research is desirable.

ABOUT THE RESEARCH COUNCIL FOR COMPLEMENTARY MEDICINE

The RCCM is a charitable organisation which promotes rigorous research in complementary therapies. As an independent body staffed by researchers, rather than practitioners, we are well-known for our neutral stance. Founded in 1983, the RCCM has supported or undertaken numerous studies including clinical trials, systematic reviews, surveys and laboratory research. One of the RCCM’s most important projects has been the development of a comprehensive bibliographic database of scientific research on complementary medicine. The RCCM is playing an active role in the Cochrane Collaboration and holds the registry of randomised trials for the complementary Medicine Field.

Andrew Vickers, RCCM

September 1997

REFERENCES

- 1 Bauer R, Jurcic K, Puhlmann J, Wagner H. Immunologische in vivo- und in vitro-Untersuchungen mit *Echinacea*-Estrakten. *Arzneimittelforschung* 1984; 38: 276-81.
- 2 Bräunig B, Dorn M, Knick E. *Echinaceae purpureae radix*: zur Stärkung der körpereigenen Abwehr bei

- grippalen Infekten. *Zeitschrift für Phytotherapie* 1992; 13(1): 7-13.
- 3 Bräunig B, Knick E. Therapeutische Erfahrungen mit Echinaceae pallidae bei grippalen Infekten. *Naturheilpraxis mit Naturmedizin* 1993; 1: 72-75.
 - 4 Schöneberger D. Einfluß der immunstimulierenden Wirkung von Pre-saft aus Herba Echinaceae purpureae auf Verlauf und Schweregrad von Erkältungskrankheiten. *Forum Immunologie* 1992; 2(8): 18-22.
 - 5 Melchart D, Linde K, Worku F, Sarkady L, Holzmann M, Jurcic K, Wagner H. Results of five randomized studies on the immunomodulatory activity of preparations of Echinacea. *J Alternat Complement Med Res Paradigm Pract Policy* 1995; 1(2): 145-60.
 - 6 Green RG, Green ML. Relaxation increases salivary immunoglobulin A. *Psychol Rep* 1987; 61(2): 623-9.
 - 7 Green ML, Green RG, Santoro W. Daily relaxation modifies serum and salivary immunoglobulins and psychophysiologic symptom severity. *Biofeedback & Self Regulation*. 1988; 13(3): 187-99.
 - 8 Johnson VC, Walker LG, Heys SD, Whiting PH, Eremin O. Can relaxation training and hypnotherapy modify the immune response to stress, and is hypnotizability relevant? *Contemp Hypn* 1996; 13(2): 100-8.
 - 9 Whitehouse WG, Dinges DF, Orne EC, Keller SE, Bates BL, Bauer NK, Morahan P, Haupt BA, Carlin MM, Bloom PB, Zaugg L, Orne MT. Psychosocial and immune effects of self-hypnosis training for stress management throughout the first semester of medical school. *Psychosomatic Medicine*. 1996; 58(3): 249-63.
 - 10 Solberg EE, Halvorsen R, Sundgot Borgen J, Ingjer F, Holen A. Meditation: a modulator of the immune response to physical stress? A brief report. *British Journal of Sports Medicine*. 1995; 29(4): 255-7.
 - 11 Hewson Bower B, Drummond PD. Secretory immunoglobulin A increases during relaxation in children with and without recurrent upper respiratory tract infections. *Journal of Developmental & Behavioral Pediatrics*. 1996; 17(5): 311-6.
 - 12 Ruzyla Smith P, Barabasz A, Barabasz M, Warner D. Effects of hypnosis on the immune response: B-cells, T-cells, helper and suppressor cells. *American Journal of Clinical Hypnosis*. 1995; 38(2): 71-9.
 - 13 Hall H, Minnes L, Olness K. The psychophysiology of voluntary immunomodulation. *International Journal of Neuroscience* 1993; 69(1-4): 221-34.
 - 14 Jasnoski ML, Kugler J. Relaxation, imagery, and neuroimmunomodulation. *Annals of the New York Academy of Sciences* 1987; 496: 722-30.
 - 15 Kiecolt Glaser JK, Glaser R, Strain EC, Stout JC, Tarr KL, Holliday JE, Speicher CE. Modulation of cellular immunity in medical students. *Journal of Behavioral Medicine* 1986; 9(1): 5-21.
 - 16 Zachariae C, Thstrup Pedersen K. Changes in cellular immune function after immune specific guided imagery and relaxation in high and low hypnotizable healthy subjects. *Psychotherapy & Psychosomatics* 1994; 61(1-2): 74-92.
 - 17 Olness K, Culbert T, Uden D. Self-regulation of salivary immunoglobulin A by children. *Pediatrics* 1989; 83(1): 66-71.
 - 18 Groer M, Mazingo J, Droppelman P, Davis M, Jolly ML, Boynton M, Davis K, Kay S. Measures of salivary secretory immunoglobulin A and state anxiety after a nursing back rub. *Applied Nursing Research*. 1994; 7(1): 2-6.
 - 19 Coates TJ, McKusic L, Kuno R, Stites DP. Stress reduction training changed number of sexual partners but not immune function in men with HIV. *Am J Public Health* 1989; 79: 885-7.
 - 20 Zachariae R, Hansen JB, Andersen M, Jinquan T, Petersen KS, Simonsen C, Taylor DN. Effects of a behavioral stress-management program on anxiety, mood, self-esteem, and T-cell count in HIV positive men. *Psychological Reports* 1995; 76(2): 451-7.
 - 21 Kiecolt Glaser JK, Glaser R, Williger D, Stout J, Messick G, Sheppard S, Ricker D, Romisher SC, Briner W, Bonnell G. Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychology* 1985; 4(1): 25-41.
 - 22 Hemila H. Vitamin C and the common cold. *British Journal of Nutrition* 1992; 67(1): 3-16.
 - 23 Hemila H. Vitamin C intake and susceptibility to the common cold. *British Journal of Nutrition* 1997; 77(1): 59-72.
 - 24 Hemila H. Vitamin C and common cold incidence: a review of studies with subjects under heavy physical stress. *International Journal of Sports Medicine* 1996; 17(5): 379-83.
 - 25 Hemila H. Does vitamin C alleviate the symptoms of the common cold?—a review of current evidence. *Scandinavian Journal of Infectious Diseases* 1994; 26(1): 1-6.
 - 26 Hunt C, Chakravorty NK, Annan G, Habibzadeh N, Schorah CJ. The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. *International Journal for Vitamin & Nutrition Research* 1994; 64(3): 212-9.

- 27 Mossad SB, Mackin ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold. *Annals of Internal Medicine* 1996; 125: 81-8.
- 28 Attenu F, Toscano G, Agozzino E, Del Giudice N. A randomized trial in the prevention of influenza-like syndromes by homeopathic management. *Revue d'Epidemiologie et de Sante Publique* 1995; 43(4): 380-2.
- 29 Ferley JP, Zmirou D, D'Adhemar D, Balducci F. A controlled evaluation of a homoeopathic preparation in the treatment of influenza-like syndromes. *British Journal of Clinical Pharmacology* 1989; 27(3): 329-35.
- 30 de Lange de Klerk ES, Blommers J, Kuik DJ, Bezemer PD, Feenstra L. Effect of homoeopathic medicines on daily burden of symptoms in children with recurrent upper respiratory tract infections. *BMJ* 1994; 309(6965): 1329-32.
- 31 Moleyar V, Narasimham P. Antibacterial activity of essential oil components. *Int J Food Microbiol* 1992; 16(4): 337-42.
- 32 Formacek V, Kubeczka KH. (1982) *Essential oils analysis by capillary gas chromatography and carbon-13 NMR spectroscopy*. London, John Wiley.
- 33 Carson CF, Cookson BD, Farrelly HD, Riley TV. Susceptibility of methicillin-resistant *Staphylococcus aureus* to the essential oil of *Melaleuca alternifolia*. *Journal of Antimicrobial Chemotherapy* 1995; 35(3): 421-4.
- 34 Ferley JP, Poutignat N, Zmirou D, Azzopardi Y, Balducci F. Prophylactic aromatherapy for supervening infections in patients with chronic bronchitis. Statistical evaluation conducted in clinics against a placebo. *Phytother Res* 1989; 3(3): 97-100.
- 35 Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. *Medical Journal of Australia* 1990; 153(8): 455-8.
- 36 Tong MM, Altman PM, Barnetson RS. Tea tree oil in the treatment of tinea pedis. *Australasian Journal of Dermatology* 1992; 33(3): 145-9.
- 37 Buck DS, Nidorf DM, Addino JG. Comparison of two topical preparations for the treatment of onychomycosis: *Melaleuca alternifolia* (tea tree) oil and clotrimazole. *Journal of Family Practice* 1994; 38(6): 601-5.
- 38 Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction on bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994; 271(10): 751-4.
- 39 Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmouth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997; 314: 722-7.
- 40 Pietroni PC. *The Greening of Medicine*. London, Gollancz (1990).
- 41 Swayne J. The cost and effectiveness of homoeopathy. *Br Homoeopath J* 1992; 81(3): 148-50.

Memorandum by the Royal College of Nursing of the United Kingdom

1. INTRODUCTION

1.1 The Royal College of Nursing (RCN) welcomes the opportunity to submit evidence to the House of Lords' Inquiry into resistance to antimicrobial agents. This issue is of increasing concern to health care professionals and the public and has significant influence on the care received by affected patients, resources utilised and effects on staff.

1.2 The focus of the evidence of the RCN to the Inquiry will be concerned with problems relating to methicillin resistant *Staphylococcus aureus* (MRSA) and infection control in hospitals. The evidence provided is anecdotal, based upon the experience of the members and advisers of the College. Many aspects of this Inquiry are of concern to the RCN but the evidence will be confined to a small number of issues, in the knowledge that the Infection Control Nurses' Association will provide a more detailed response in writing and in person.

1.3 The RCN evidence will focus upon:

- The effects of MRSA colonisation on hospital in-patients.
- The effects of MRSA colonisation/infection on patients in the community.
- The effects of MRSA colonisation/infection on health care staff.
- Management issues.

2. EFFECTS OF MRSA COLONISATION/INFECTION ON HOSPITAL IN-PATIENTS

2.1 The RCN is concerned that the acquisition of MRSA by hospital in-patients may be detrimental to their physical and mental well-being in a number of ways.

2.2 Patients with MRSA are invariably nursed in isolation, either in single rooms, cohorted in a bay or in an isolation unit. This experience cuts them off from the companionship of other patients; restricts access to staff; limits access to facilities such as the mobile telephone, newspapers, hairdresser etc; prevents the measurement of their own progress against others with similar conditions; and visits by friends and family may be reduced due to fear, lack of knowledge or confined space.

2.3 Patients nursed in isolation may also have less access to therapies which may promote their rehabilitation and hasten their discharge, such as physiotherapy and occupational therapy. These therapies may be attempted within the isolation room, rather than in the specialist department where the necessary space and apparatus would be available.

2.4 We are aware of patients who have acquired MRSA in hospital who have subsequently had prescribed treatment and surgical interventions postponed or cancelled as a result. It is unfair that patients who have a hospital acquired infection are discriminated against in this way.

2.5 It is often hospital policy that three consecutive negative microbiological screens are required before the patient may leave isolation. In some patients, with chronic wounds such as leg ulcers and tracheostomies, or devices such as urinary catheters, Hickman lines or PEG tubes, it is more difficult to eradicate MRSA. The patient may be colonised for weeks or months and therefore isolation is prolonged and may cause emotional distress. In addition, standard infection control precautions usually require the wearing of latex gloves, plastic aprons and sometimes face masks, all of which limit human contact even further and may be detrimental to the patient's health.

2.6 Some patients become colonised with MRSA and require only the application of topical agents, while others develop infection and require systemic treatment in addition. Antibiotic therapy may need to be administered intravenously, the drugs are expensive and can have unpleasant side-effects, sometimes requiring regular blood tests to check therapeutic levels. These costs and ill effects can be avoided if MRSA is prevented.

3. EFFECTS OF MRSA COLONISATION/INFECTION ON PATIENTS IN THE COMMUNITY

3.1 The increasing incidence of MRSA is also having an impact on primary health care. Practice nurses and district nurses often have to continue treatment and care regimes post-discharge, increasing their workload and costs of their interventions.

3.2 We are also aware of several patients who have been removed from General Practice lists following the acquisition of MRSA. The reasons for this may be ignorance of the organism or fears regarding the costs of continuing care.

3.3 There have also been many instances where patients with MRSA have been refused a place in a nursing or residential home. The matrons and owners state that their insurance does not include cover for the management of MRSA. As caring environments, it is inevitable that their clients will develop infection at some time during their stay. Certain infections, such as MRSA, gastro-enteritis, influenza etc, may spread and insurance policies should meet all these eventualities.

3.4 Even those patients living in their own homes, who only need social care from home carers, have suffered as a result of acquiring MRSA. It is not uncommon for carers to refuse to visit these patients in case they acquire MRSA themselves and take it home to their families. This action is often the result of misinformation or lack of training. All individuals employed as carers should receive training in infection control procedures relevant to their area of work so that they may practice safely and confidently. This may include hand hygiene, general hygiene, use of protective clothing, laundering, disposal of waste.

4. EFFECTS OF MRSA COLONISATION/INFECTION ON HEALTH CARE STAFF

4.1 In the event of an outbreak of MRSA nurses, and other staff, may become colonised or infected themselves. This is particularly likely if they have chronic skin conditions, such as eczema, or structural nasal problems. Most affected staff are easily treated with topical treatment or oral antibiotics and do not have to stop working. However, a number become chronically colonised and repeated treatments fail to eradicate the organism. These staff members may have to stop work whilst receiving treatment in order to reduce the risks of transmission to patients. Some are re-deployed to non-clinical areas. However, re-deployment is not always possible due to the employee's skills, attributes and abilities etc.

4.2 MRSA is not a registered industrial disease therefore if an employee is eventually dismissed as a result of MRSA he or she cannot receive benefit. Some employers, and some countries, will not employ staff who have, or who have had, MRSA and therefore the long-term employment prospects for these individuals are seriously impeded.

5. MANAGEMENT ISSUES

5.1 The management of MRSA may be adversely affected by a number of factors such as: poor staff/patient ratio; frequency of patient transfers between hospital wards; poor environment including the design of wards and standards of hygiene; lack of facilities for isolation including en-suite single rooms with appropriate air handling; the use of agency staff who move between hospitals and wards without a good knowledge of the patients and hospital policies.

5.2 The role of infection control nurses, doctors and laboratories in the management of MRSA is crucial, and their workload has increased dramatically in recent years without a corresponding increase in resources. Infection Control Nurses are required to support nurses, patients, housekeepers and other staff and provide education and advice on infection control practice. They carry out surveillance of MRSA, as well as other infections, and develop MRSA policies and reports for their units. This is essential work, but diverts attention and resources away from the many other important infection control activities they should also be undertaking.

5.3 The closure of wards—to control outbreaks or facilitate additional cleaning—is costly and disruptive to all concerned. Admissions may be postponed, contracts not met and the trust may receive adverse publicity. Patients may complain that they should not have been exposed to MRSA and may even resort to litigation. However, it is difficult to avoid MRSA when the incidence is high. Wards in all local trusts may be affected and if the risks of cancelling a repair of a fractured neck or femur are weighed against the risks of MRSA, it is more important to proceed with the operation.

6. RECOMMENDATIONS

6.1 The Royal College of Nursing recommends that the following actions are taken to measure the impact of MRSA, reduce the incidence and equip those concerned with the necessary knowledge, skills and resources.

- More research should be undertaken to measure the incidence of MRSA, the impact of MRSA on hospital and community staff, the role of colonised staff in the spread of the organism, the risks of transmission to family members and the effectiveness of current infection control practices.
- Development of national policy and standards for the management of MRSA.
- Development and monitoring of national standards for hospital hygiene.
- Development and monitoring of national standards for hand hygiene.
- Formalise the status of staff chronically affected by MRSA.
- The training of all health and social care staff in infection control procedures.
- Adequate resourcing of infection control departments and laboratories.
- National public information campaign to address misinformation through the media.

Memorandum by Professor Ian Phillips and Professor Colin Roberts, Royal College of Pathologists

ANTIBIOTIC RESISTANCE

Antibiotic resistance is presumably as old as antibiotics themselves, as a means by which antibiotic-producing organisms protected themselves from their harmful effects. With the advent of antibiotics as therapeutic substances, these resistance mechanisms were probably transferred to pathogenic organisms and were augmented by mechanisms arising in situ, giving rise to the rich variety of antibiotic resistance that we now recognise. It is the purpose of this paper to summarise the epidemiology of these mechanisms as observed by medical scientists and practitioners during the antibiotic era, and to suggest necessary action to achieve a measure of future control.

THE PAST

Examples of antibiotic resistance were reported by Fleming in 1929 in his first paper on penicillin: he showed that while Gram-positive organisms such as streptococci and staphylococci were sensitive to the new agent, others, and particularly the Gram-negative “coli-typhoid” group and the organism that is now known as *Haemophilus influenzae*, were inherently resistant. The first example of resistance in a clinical setting is thought to be in the report on the treatment of gonorrhoea by Crean in 1936, in which individuals were described who failed to respond to doses of sulphonamide that cured the majority.

The first example of the failure of penicillin in a major clinical context was in the treatment of staphylococcal infection. *Staphylococcus aureus* was originally almost always sensitive and therefore susceptible to penicillin, but with the increasing use of the agent after the Second World War increasing numbers of refractory cases of infection were seen and it became clear that more and more strains of the organism produced β -lactamase (an enzyme which destroys penicillin) and thus had acquired resistance to penicillin. Within a decade, most cases of staphylococcal infection acquired in hospitals were caused by strains resistant to penicillin, and after a further decade virtually all isolates of the organism, in hospital and

in the community, were resistant to penicillin. Paradoxically, some other important pathogens behaved differently: for example, another Gram-positive species, *Streptococcus pyogenes* (the infamous “flesh-eating virus” of the tabloid press, but less dramatically the cause of many sore throats and less serious skin infections) did not acquire resistance to penicillin at that time and has not done so now.

Soon after the introduction of penicillin into clinical practice other antibiotics, often active on a wider range of organisms (broad spectrum), were discovered and developed for clinical use. Penicillin-resistant *Staphylococcus aureus* was an obvious indication for their use, but this organism acquired and retained resistance to each new antibiotic in turn. The “Hospital Staphylococcus” of the 1950s and 1960s, particularly able to spread from one person to another, was at its worst often resistant to penicillin, streptomycin, tetracycline, erythromycin, and sometimes to other agents, necessitating the use of vancomycin as a last resort. It was in this context that the first semi-synthetic antistaphylococcal antibiotic, methicillin, was developed and introduced by the British pharmaceutical company Beecham. At first it seemed that this antibiotic too was doomed, since resistant strains were very soon found in hospitals. However, this was not to be so serious a problem—at least at that time—since the resistant strains failed to establish themselves with any success. At much the same time, the “Hospital Staphylococcus” also began to decline, and the 1970s were strangely free from epidemic staphylococcal hospital infection. The staphylococcus taught us much about the epidemiology of resistance, especially its ability to spread among organisms and thus to affect patients, at least in a hospital setting, and it was in relation to staphylococcal infection that the first antibiotic policies for the more rational use of these therapeutic agents were devised as well as the infection control protocols and practices (based in turn on war-time experience of *Streptococcus pyogenes*) required to limit its spread. It also taught us that resistance can sometimes disappear despite antibiotic selective pressures that would seem ideal to enable it to survive and flourish, presumably because of changes in virulence and even less well characterised changes in ability to spread among individual strains.

As the staphylococcus declined, the Gram-negative organisms gained in importance. Organisms from this group had always been responsible for important infections in the community such as urinary tract infection and gastroenteritis—the latter often caused by bacteria acquired from animals (a subject not pursued further here). The former is usually caused by *Escherichia coli*, and it too has slowly but inexorably become more resistant to antibiotics—for example to ampicillin, another Beecham antibiotic introduced in the early 1960s, at the rate of about 1 per cent per annum. It was among the Gram-negative organisms that transferability of antibiotic resistance between different species was first described in a clinical setting. The gonococcus added the ability to produce beta-lactamase to several other resistance mechanisms by this means in the 1970s. A variety of other Gram-negative organisms, including *Pseudomonas aeruginosa*, gained a foothold in hospitals, taking advantage of opportunities afforded by advances in the management of critically ill patients, who were not only immunocompromised but increasingly concentrated in intensive care and other specialised units. Many of these opportunistic pathogens are characteristically resistant to the normal antibiotics and the pharmaceutical industry (increasingly in Japan) produced many new agents directed against them. In turn, the bacteria developed their inevitable response of further resistance. At the same time, and in the same context, serious fungal infections have become more common and resistance to several of the small number of antifungal agents, particularly the useful azoles, has been described.

The past decade has been characterised by resistance among organisms causing infections primarily in the community, little affected previously. Among the major respiratory pathogens, the pneumococcus has increasingly acquired resistance to penicillin and other antibiotics and *Haemophilus influenzae* resistance to ampicillin. *Mycobacterium tuberculosis* has increased in prevalence and in resistance, particularly among those who do not comply with treatment or whose natural defences are damaged (for example by HIV infection). Limited success with the introduction of antiviral agents has appeared to spare the viruses from the problem of acquired resistance, but the remarkable advances in the chemotherapy of viral infections, including HIV infection, have now provided a number of examples. Finally, the parasitic diseases, which have been relatively neglected in the search for new chemotherapeutic agents, have also in recent years provided important examples of resistance, none more important than malaria.

The past has therefore taught us that resistance mechanisms exist or can be assembled for any antibiotic, natural or synthetic, and that when antibiotics are used in clinical practice, and seemingly in proportion to the amounts used, these mechanisms will often become increasingly prevalent, sometimes slowly, sometimes rapidly, and will often cumulate to produce multiple antibiotic resistance. These multiply-resistant organisms often spread within and between countries.

For a variety of reasons, antibiotic resistance may appear to have little clinical importance. In some cases, antibiotic doses may be readily and safely increased, but always within limits, to achieve cure, as with penicillin in gonorrhoea, while in others, patients may recover spontaneously or with minimal contribution from antibiotic treatment as with many cases of simple cystitis. This has caused some medical practitioners to deny the importance of antibiotic resistance, especially during the period when many new agents were being produced, and the older agents could be abandoned for the treatment of common infections: in the longer term, this may well prove to have been misguided, particularly as the supply of truly new antibiotics, unaffected by current resistance mechanisms, has diminished.

THE PRESENT

It is generally apparent that we are at present in a phase of active diversification of antibiotic resistance both in hospitals and in the community outside.

The β -lactam drugs—including the penicillins, cephalosporins and carbapenems, which are the mainstay of antibiotic therapy—are particularly under threat. In some Gram-negative bacteria, particularly common in hospitalised patients, potent chromosomally-mediated β -lactamases are produced in large amounts, enabling species or strains that possess them to resist the newer cephalosporins developed to treat infections caused by them. In other Gram-negative bacteria, mutations in the transferable plasmid genes that mediate other types of β -lactamase production have produced variant enzymes that attack newer as well as older penicillins and cephalosporins, rendering them ineffective. Even the hitherto unaffected carbapenems are attacked by another set of newly evolving enzymes at present still rare, at least outside Japan. Among the Gram-positive bacteria, β -lactam resistance is largely following a different course depending on changes in the proteins that bind these drugs to susceptible bacteria. Methicillin-resistant *Staphylococcus aureus* (MRSA) currently such a scourge in many hospitals and nursing homes, arises as a result of such a change in a penicillin-binding protein, affecting all beta-lactams, while increasingly the pneumococcus, the major cause of pneumonia and an important cause of meningitis, is becoming resistant to penicillin, the best antibiotic until now for its treatment, and to newer beta-lactams.

Nor are the other classes of antibiotics, introduced to replace β -lactams or for the treatment of infections due to organisms inherently insusceptible to them, being spared. Vancomycin, for so long the antibiotic of last resort for the treatment of infections caused by multiply-resistant Gram-positive organisms, is currently under active threat for the treatment of serious infections caused by enterococci, mostly acquired in hospitals and increasingly often resistant to vancomycin, and also for the treatment of infections caused by *Staphylococcus aureus*, according to reports of staphylococci of diminished sensitivity (VIS) from Japan, the USA and from eastern Europe within very recent months. In each case, infections caused by these organisms are potentially untreatable by any licensed antibiotics. Macrolides (such as erythromycin, and more recent agents in this class) and the new quinolones introduced within the last decade, are also threatened by resistance, affecting their use or potential use for some of our commonest infections, such as pneumonia (especially when due to intrinsically penicillin-resistant organisms such as *Legionella pneumophila*, mycoplasmas or other atypical pathogens), exacerbations of chronic bronchitis, sinusitis, otitis media and urinary-tract infections.

Recent reports have reminded us that diseases often thought to have disappeared by the general public, not only have not done so but may have increased in prevalence aided by antibiotic resistance. Perhaps the most alarming is drug-resistant tuberculosis of which there have been recent instances of hospital infection in Britain among immunocompromised patients. From more distant parts of the world, but of importance to us if only because they might be imported into Britain, come recent reports of antibiotic resistant typhoid, dysentery, cholera and plague, while the existence of chloroquine-resistant malaria is a threat to all who live in tropical countries (including, possibly, Britain in which malaria transmission is a distinct possibility if global warming takes a hold) and all who travel to them.

Finally, one of the topics of greatest fascination at the moment is the role of micro-organisms in a variety of chronic diseases, including cancer, coronary artery disease and gastric diseases. In some cases, antibiotic treatment has been shown to be effective, but already resistance has been reported, as for *Helicobacter pylori* in stomach diseases. Clearly, extreme vigilance will be required if we are not to lose new opportunities for therapy as soon as they are introduced.

THE FUTURE

Our institutions must be able to resolve current problems in antibiotic resistance and be able to respond to others as they arise, sometimes as emergencies. It may require considerable educational effort to persuade some of them that the resources needed could not be better spent elsewhere, even to the extent of their gaining support within the medical and academic community for the proposition that no problem exists, or that it has been much exaggerated.

Medical research. Requests for funding from the major research bodies for research into antibiotic resistance clearly cause problems in relation to funding policy and practice. It appears that *fundamental* research into antibiotic resistance does not often recommend itself to peers. Projects on pathogenicity are more likely to prove fundable. The climate is such that many who would apply, decide not to do so because they are reluctant to waste their own and funders' time—and this despite funders' stated wish, at least from time to time, to support such work. Pressures from deans on medical academics to get as much funding as possible from the MRC or Wellcome, linked with punitive reductions in resources when they fail to do so, are already exacerbating the general shrinkage that has taken place in the relevant section of the medical academic community. The problem with funding for *applied* research from these bodies is even greater: not uncommonly applications fail on the grounds of insufficient relevance to the practice of medicine, clearly based on the views of short-sighted or even ignorant peer-reviewers. There is also the feeling that if such research were supported the funding might more appropriately come from the NHS or from the Pharmaceutical Industry. Indeed, the NHS does fund such work, but support appears to depend on

individual directors of research and may thus be patchy. To its credit, industry also supports this type of work, but is naturally disposed to allocate funds either to more fundamental work leading to new modes of therapy or to work that demonstrates efficacy and safety of developed products.

We commend the apparently outmoded concept of well-founded diagnostic laboratories alongside appropriate clinical facilities; these should be strategically sited in selected hospitals, adequately staffed (by university, NHS and PHLS) and funded (by these same bodies); able to carry out appropriate surveillance (a subject which would benefit from more collaborative and academic input, for example to define appropriate denominators and appropriate sampling methods); with results nationally and internationally co-ordinated (generally by the PHLS in collaboration with professional groups such as The British Society for Antimicrobial Chemotherapy or the European Society for Clinical Microbiology and Infectious Disease); ready to define problems when and where they arise; and able to make persuasive applications for appropriate research funding to seek out solutions to more fundamental problems, or to pass them on to a smaller number of larger centres when the work needed requires specialised and integrated resources.

We also recommend that funding bodies examine carefully the general research needs in this area, and do not depend on quixotic reviewers for critical opinions. We identify a need for critical examination of current assumptions on the efficacy of diminished use of individual antibiotics or groups of antibiotics in reversing resistance trends (one of the bases of many antibiotics policies), study of the potential for direct reversal of resistance (for example, by genetic manipulation of translation of genetic codes), thorough examination of the potential for vaccines, collaboration with industry in antibiotic discovery, research on the prevention of emergence of resistance in chronic microbial disease, and critical study of the concept of drugs with a narrower spectrum.

Diagnostic and Clinical Practice. If antibiotic resistance is to be controlled, the NHS will need to improve existing diagnostic and clinical facilities, ensuring particularly that rapid specific microbial diagnostic tools are available, and that isolation facilities and arrangements for antibiotic trials to assess the clinical significance of in-vitro resistance are adequate. It may be necessary for the medical profession to redefine these needs under the leadership of the Royal Colleges.

It will also be necessary to ensure the continuing strength of clinical microbiology laboratories, with appropriate medical and scientific staff (as defined, for example, by the Association of Medical Microbiologists). Their task is to collaborate in work to develop agreed and improved methodology for antibiotic sensitivity testing, since methods in current use are often inadequately controlled, and produce results that have only local validity. The British Society for Antimicrobial Chemotherapy needs support in its attempts to improve standards, and the European Society for Clinical Microbiology and Infectious Diseases in its attempts to define comparability of the different methods used in Europe. Attempts to impose a single international method should at present be resisted, since no such method acceptable to all, or even most microbiologists in Europe exists. They will also be needed to collaborate in surveillance and introduce improved reporting arrangements as methods are developed.

Finally, it will also be necessary to ensure that appropriate infection control arrangements are in place—they are well defined and agreed—and to ensure that antibiotic prescribing policies are driven on the basis of full cost-effectiveness assessments, which include the effects of antibiotic resistance and measures designed to prevent it, rather than simply on primary costs of therapy. Again there may be a need for research to refine the methods of defining such policies and ensuring that they are effective, the latter to be taken up by medical audit.

Education. Medical microbiologists and infectious diseases practitioners recognise their duty to educate both undergraduates and postgraduates so that they understand the origins of antibiotic resistance and the role of every prescribing doctor and of their own specialities in its surveillance and control. Senior medical academics and NHS managers must be persuaded to continue to support them in such activities, appreciating their different roles, and to understand the interdependence of research, medical practice and education for these practitioners.

The role of Government. Through national and international agencies, Government should ensure that the structures required to address the needs outlined above are in place and effective. These involve:

Health, particularly in relation to diagnostic and epidemiological functions in laboratories serving our hospitals and primary care (including, but not exclusively the PHLS), to the care of patients with infections, to Health Services research, and to training and education of staff.

Education and Science, in relation to adequate staffing and resourcing of University departments involved in basic and applied research on antibiotic resistance (some at least being academic diagnostic and infectious disease departments) and to effective support for their role in education.

Regulatory bodies, in relation to antibiotic registration (involving the Medicines Commission and the European Medicines Evaluation Agency, working with the advice of professional bodies directly involved in antibiotics), standardisation (BSI, CEN and ISO are all working on methodology and standardisation of antibiotic sensitivity testing, with different, and sometimes conflicting advice from professional bodies), Health and Safety (increasingly involved in outbreaks of infection).

CONCLUSION

The best scientific evidence is required to answer the issues referred to above. Well controlled studies will be required to address them, and the effect of new processes and strategies on morbidity and mortality as well as their economic impact. These are likely to be complex and expensive studies but would be an effective way to gain reliable insight into the extent and development of the threat of antimicrobial resistance and rational strategies for addressing the challenge.

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Memorandum by the Royal Pharmaceutical Society of Great Britain

The Royal Pharmaceutical Society is incorporated by Royal Charter as the registration and professional body for pharmacists in Great Britain in all aspects of practice of the profession, and the promotion of pharmaceutical education and the application of pharmaceutical knowledge. The Society welcomes the opportunity to respond to the invitation of the Sub-committee 1 of the Science and Technology Committee to submit evidence on resistance to antimicrobial agents. It has previously submitted evidence to the Swann Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (November 1969).

1. The Royal Pharmaceutical Society has concern about the threat to public health posed by the re-emergence of a number of major infections as substantial threats to public health and the development of resistance of the causative organism to currently-available antimicrobial agents, both in this country and world-wide. The Society has consulted a number of specialists in this field and is pleased to offer information in the areas of:

- the development of resistance to antimicrobial agents;
- the monitoring of resistance;
- the role of the hospital pharmacist;
- the role of the community pharmacist;
- the role of industry in the development of alternative strategies for dealing with infections caused by microbes; and
- two specific disease entities, namely malaria and tuberculosis.

DEVELOPMENT OF RESISTANCE

2. The Society notes with concern the problem of increasing levels of resistance for some organisms. To illustrate the extent of the problem, we quote a recent report on the incidence of occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) found in samples of blood and cerebrospinal fluid of hospitalised patients and monitored over the period 1989-95. The incidence remained stable (at 1.5 per cent of isolates) over the period 1989-91; thereafter it rose to 13.2 per cent in 1995. The resistance to six other commonly-used antibiotics increased significantly over the same period and there was a trend for methicillin-resistance to be linked to resistance to other antibiotics (Speller et al, 1997).

3. The introduction of antibiotics into clinical medicine has produced great benefits to mankind but has also brought about a wide range of unforeseen problems. Apart from potential toxicity or, with some antibiotics, hypersensitivity reactions, several bacterial species now show high resistance to many drugs. Furthermore, the transferability of resistance from resistant to sensitive cells of the same or different species or genus is a well-known phenomenon with potentially serious clinical consequences. Ways of overcoming such resistance are needed urgently (Tenover & McGowen, 1996; Russell & Chopra, 1996).

Bacteria may also not be susceptible to some types of biocides (antiseptics, disinfectants and preservatives) (Russell & Chopra, 1996) and the possibility exists of a link between antibiotic resistance on the one hand and biocide resistance on the other (Russell, 1997).

4. *Bacteria Resistant to Antibiotics*. Currently, there is considerable concern about antibiotic-resistant bacteria such as *Staphylococci*, *Enterococci* and *Mycobacteria*, multidrug-resistant Gram-negative pathogens and "emerging" pathogens such as *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Enterobacter* spp. Some of these are considered below.

5. *Mycobacteria*. In recent years, there has been a global resurgence of tuberculosis (WHO Report, 1996). This is closely associated with the pandemic of AIDS whereby the depressed cell-mediated immunity leads either to reactivation of a previously latent *Mycobacterium tuberculosis* infection or susceptibility to a newly acquired infection. A major problem associated with therapeutic regimens is the long period of treatment required for a successful outcome. Although adherence to a treatment regime can be maintained for a hospitalised patient, many AIDS patients in the community fail to complete a course of anti-tuberculous therapy. Furthermore, in Third World countries the time taken for confirmation of infection and susceptibility-testing of isolates is often so long that contact with the individual cannot be effectively maintained, making it difficult to ensure that the correct medication is delivered to the non-hospitalised patient.

Such non-adherence results not only in continued infectivity but also in the selection of drug-resistant organisms, leading to the emergence of multigrade *M. tuberculosis* (MDR TB) strains in the community. These organisms can spread to the hospital environment when AIDS patients are admitted for acute care.

Intrinsic resistance of *Mycobacteria* to antibiotics associated with the complex mycobacterial cell wall (Jarlier & Nikaido, 1990; Zhang & Young 1994). In essence, the wall consists of peptidoglycan covalently linked to a polysaccharide co-polymer (arabinogalactan) esterified to fatty acids (mycolic acids). Complex lipids, lipopolysaccharides and proteins are also present (Inderlied et al 1993). Porin channels have been identified (Nikaido et al, 1993), but appear to permit the entry of only very small hydrophilic antibiotics, undoubtedly an important factor in the intrinsic resistance of *Mycobacteria* to hydrophilic drugs. Cell wall composition of a particular species has been found to be influenced by its environmental niche. Interestingly, derivatives of isoniazid (isonicotinyl hydrazine) that are more hydrophobic than isoniazid itself have greater anti-tubercular action (Zhang & Young, 1993, 1994).

Acquired resistance of *Mycobacteria* to antimycobacterial drugs is a well-known phenomenon (Barry & Mdluli, 1996). It is probable that expression of the gene *kata*, which encodes an enzyme having catalase and peroxidase activities in *M. tuberculosis* is important in isoniazid activity; this enzyme is believed to convert isoniazid into an active form that interferes with mycolic acid biosynthesis. Deletion of *kata* results in loss of isoniazid sensitivity, whereas transformation of the gene into isoniazid resistant mutants restores susceptibility.

Mycobacteria are resistant to many types of biocides, including dyes, chlorhexidine and quaternary ammonium compounds (Russell, 1996). Recently, strains of *M. chelonae* subspecies *Abscessus*, isolated from endoscope washes, have been found to be highly resistant to glutaraldehyde, and possibly to peracetic acid also (van Klingeren & Pullen, 1993; Griffiths et al 1997). Reasons for this high resistance are unknown. This organism has a particularly propensity for adhering to smooth surfaces.

Recommendations. It is recommended that:

- (i) further research be undertaken on cell wall components involved in resistance to antibiotics and biocides;
- (ii) further research be conducted on how drugs are transported across cell walls;
- (iii) reasons for the high resistance of *M. chelonae* to glutaraldehyde be sought; and
- (iv) improved and faster methods for testing for mycobacterial sensitivity are developed.

6. *Methicillin resistant Staphylococcus aureus (MRSA)*

Staphylococci are members of a group of invasive Gram-positive pyogenic cocci that can cause acute to chronic infections in man, ranging from surgical sepsis to generalised septicaemia and bacteraemia (Hackbarth & Chambers, 1989). Although benzylpenicillin initially offered effective treatment for severe infections caused by invasive staphylococci, such as *S. aureus*, within a few years the majority of hospital isolates were resistant by virtue of expressing β -lactamase activity. The introduction of other types of antibiotics also resulted in the emergence of staphylococcal strains specifically resistant to these antibiotics and, because of β -lactamase production, often resistant to benzylpenicillin also (Russell & Copra, 1996).

The introduction of β -lactamase-stable penicillins such as methicillin caused a major decline in the incidence of multiple-resistant *S. aureus* strains in the 1960s. Later, however, strains of *S. aureus* (known as MRSA) resistant to multiple antibiotics, including methicillin and gentamicin, emerged that were responsible for global outbreaks of hospital infections.

Few antibiotics remain effective against such strains and one of these, vancomycin (a rather toxic antibiotic requiring intravenous administration) is now under threat because vancomycin-resistance has been transmitted from vancomycin-resistant enterococci (VRE) into *S. aureus* (Williams et al, 1997).

β -lactam resistance in MRSA strains is mediated by the *mec* determinant in which resistance arises from the biosynthesis of a unique penicillin-binding protein (PBP2') which has a low affinity for β -lactams. Some strains of MRSA, notably EMRSA-15 and EMRSA-16, have an extraordinary ability for hospital-wide spread.

It has been proposed that, since resistance to what are termed "nucleic acid-binding compounds" (chlorhexidine, quaternary ammonium compounds, acridines, amidines) was prevalent in the staphylococcal population long before gentamicin resistance was found in MRSA, then biocide resistance could be of particular significance in terms of the potential for the survival of these strains in the hospital environment (Lyon & Skurray, 1987). The coagulase-negative cocci are emerging as effective pathogens in medical device-related infections. Their capacity to establish biofilms on surfaces, a characteristic shared (but to a lesser extent) with *S. aureus*, confers an intransigence to antibiotic challenge. This phenotypic characteristic augments other mechanisms of resistance.

Recommendations. It is recommended that:

- (i) monitoring of the emergence of vancomycin-resistant MRSA be undertaken as a matter of urgency; and
- (ii) studies be carried out to determine whether low concentrations of biocides can select for the survival of antibiotic-resistant *Staphylococci*.

7. *Vancomycin-resistant enterococci (VRE)*

The three most important species of enterococci, *Enterococcus faecalis*, *E. faecium* and *E. durans*, are found in the human and animal gut. Enterococci may cause urinary and abdominal wound infection and glycopeptide-resistant strains are becoming a matter of increasing clinical concern. Strains may also show high-level resistance to aminoglycoside antibiotics.

High-level resistance to vancomycin (van B phenotype) involves several genes, which specify the conversion of pyruvate to lactate, the biosynthesis of the depsipeptide D-Ala-D-Lac and the hydrolysis of D-Ala-D-Ala, thereby eliminating normal peptidoglycan precursors. High-level resistance is induced by both vancomycin and teicoplanin and is mediated by transposon *Tn* 1546 or related transposons (Arthur et al, 1996; Courvalin, 1996).

Moderate- to high-level vancomycin resistance (van B phenotype) also involves the production of D-Ala-D-Lac but is inducible by vancomycin and not teicoplanin.

Low-level resistance to vancomycin (van C phenotype) involves the production of D-Ala-D-Ser and is believed to be constitutive and chromosomally controlled. Resistance to teicoplanin is not found.

There does not appear to be any correlation between VRE or aminoglycoside resistant strains and biocide resistance (Alqurashi et al, 1996; Anderson et al, 1997).

Recommendations: It is recommended that:

- (i) uptake of drugs and biocides into VRE be investigated;
- (ii) the reasons for the greater efficacy of teicoplanin, compared to vancomycin, against vanB and vanC phenotypes be studied; and
- (iii) that teicoplanin analogues whose binding is unaffected by D-Ala-D-Lac be produced.

8. *Multidrug-resistant Gram-negative bacteria*

Multidrug resistance is a serious problem in enteric and other Gram-negative bacteria (Levy, 1992; George, 1996). As distinct from plasmid-mediated resistance, multiple-drug resistance is a term employed to describe a resistance mechanism by genes that comprise part of the normal cell genome. These genes are activated by induction or mutation caused by some types of stress; because the genes are ubiquitously distributed, there is no need for genetic transfer.

Exposure to a single drug can lead to resistance not only to the drug but also to chemically-unrelated drugs. For example, chromosomal multiple antibiotic-resistant mutants of *Escherichia coli* selected by low concentrations of chloramphenicol or tetracycline are much less sensitive to fluoroquinolones than wild-type *E. coli*, with the frequency of emergence at least 1,000-fold higher than with norfloxacin selection.

The multiple antibiotic-resistant regulatory chromosomal locus is widespread among enteric bacteria (George, 1996). Mechanisms of resistance do not involve drug modification or inactivation but are demonstrable as decreased uptake, increased efflux or both. For example, tetracycline accumulation in high-level multiple antibiotic-resistant mutants is greatly reduced and an energy-dependent tetracycline efflux system can be demonstrated in whole cells and in everted membrane vesicles prepared by lysis of *E. coli* cells (Levy, 1992; George, 1996).

Overall, multiple antibiotic-resistance is widespread among Gram-negative bacteria and poses a major chemotherapeutic problem particularly when such organisms can acquire R (resistance) plasmids that supplement this drug resistance.

Recommendation: It is recommended that:

- (i) the effects of biocides on multiple antibiotic-resistant strains be studied.

9. Possible Linked Antibiotic-Biocide Resistance

Antibiotics usually have a specific site or mode of action whereby they achieve a selective toxic effect against bacteria but not human host cells. By contrast, biocides frequently have multiple target sites in the bacterial cell and by their very nature are often toxic not only to bacteria and other micro-organisms but also to host cells. Thus, mutation at, or absence of, a normal target site (or the presence of an additional target site) may be responsible for producing resistance to antibiotics but not to biocides (Russell & Chopra, 1996).

An association between antibiotic resistance and chlorhexidine and quaternary ammonium compound resistance to *Providencia* species has been observed but no evidence of a plasmid link obtained (Stickler & King, 1992). Numerous reports have linked the presence of plasmids conferring antibiotic resistance to cationic biocides (chlorhexidine, quaternary ammonium compound, diamidines and acridines, as well as to ethidium bromide) in MRSA strains (Littlejohn et al, 1992; Paulsen et al 1996a; Paulsen et al 1996b). Generally, it has been found that elevated minimum inhibitory concentrations of biocides are observed in such strains (Littlejohn et al 1992), although they are inactivated just as readily as methicillin-sensitive *S. aureus* (MSSA) strains by chlorhexidine (Cookson et al, 1991).

The possession of *qac* genes in MRSA (and methicillin-resistant *S. epidermidis* (MRSE)) has been claimed to give these organisms the ability to survive in inimical conditions (Stickler & King, 1992; Littlejohn et al 1992; Paulsen et al 1996). It is unclear, however, as to the low-level efflux resistance encoded to biocides by these genes is of relevance in the clinical context where much higher concentrations of chlorhexidine and quaternary ammonium compound are employed.

Recommendations: It is recommended that:

- (i) there is an urgent need to provide information about the bactericidal, as opposed to bacteriostatic, activity of chlorhexidine, quaternary ammonium compounds and other biocides on MRSA and MRSE possessing *qac* genes;
- (ii) activity of biocides against multidrug resistant Gram-negative bacteria, where multi-drug efflux exporters are responsible for resistance, should also be examined critically;
- (iii) suitable new disinfection policies may have to be produced and the usage of skin antiseptics reviewed; and
- (iv) the clinical relevance of a possible association between antibiotic resistance and biocide resistance be assessed forthwith

MONITORING OF RESISTANCE

10. The Society believes that it is critically important to have in place monitoring systems which routinely record the pattern of use of individual antibiotics and also the susceptibilities of individual organisms to each antibiotic.

Recommendation: It is recommended that monitoring systems to record the pattern of antibiotic usage are in place

11. The PACT data which is available from the Prescription Pricing Authority record the actual prescribing figures for individual antibiotics and allows the extent of usage of newer antibiotics to be monitored, following their introduction. Table A shows the increase in numbers of antimicrobial agents that has occurred over the period 1968–97. The figures show that the increase in the total number of antibiotics listed in the British National Formulary rose from 26 in 1968 to 79 in 1988, with 80 listed in the current edition (September 1997).

12. Some centres (such as that at University College Hospital, London) hold records of sensitivities to individual antibiotics. These records (since 1971) show that sensitivity of urinary pathogens to ampicillin and amoxicillin has continued to fall both in general practice and in hospital. Sensitivity to ciprofloxacin was greater than for any other antibiotic and there was no evidence of any increase in resistance (Grüneberg, 1994). It is essential that these data continue to be available, to inform decisions on antibiotic use. The major areas of current concern in hospitalised patients are as follows:

- Methicillin-resistant *Staphylococcus aureus*;

- MRSA with enhanced epidemicity (EMRSA);
- Glycopeptide-resistant *Enterococci*, including Vancomycin-resistant *Enterococci* (VRE).

HOSPITAL PHARMACY

13. Hospital pharmacists have a substantial part to play in the limitation or prevention of the development of resistance of micro-organisms to antimicrobial agents in a hospital environment. Their roles are two-fold. Firstly, to work with clinicians and microbiologists in the development of policies for the rational use of antibiotics, based on the best scientific data, and the creation of antibiotic formularies. Secondly, to implement these policies and to monitor usage of antibiotics so as to inform future decisions.

14. Hospital pharmacists work closely with microbiologists on hospital drug and therapeutic committees to formulate antibiotic prescribing policies. The criteria used for selection of the most appropriate antibiotic are (i) efficacy, the agent which is most likely to treat the diagnosed infection, preferably based on laboratory sensitivity results, but otherwise taking into consideration local resistance patterns; (ii) safety, that is, the agent with the least side effects. When these criteria are fulfilled then (iii) cost is considered; given equal safety and efficacy then the most cost effective antibiotic will be selected, taking into account the cost of laboratory tests and monitoring, and administration.

15. Hospital pharmacists also serve on infection control committees and contribute advice on the following:

- availability and safe use of disinfectants and antibacterial agents;
- providing prophylaxis for staff suffering personal injury by needlestick injury contaminated by blood from a high risk patient, such as patients with suspected HIV or Hepatitis B;
- personal hygiene—hand washing and use of surgical scrubs and skin preparation solutions; and
- aseptic and barrier procedures.

16. Factors which hinder the control of MRSA in the current UK “market-led” health care delivery system have been reported as follows:

- (i) shortage of hospital beds;
- (ii) patients moving from ward to ward;
- (iii) increase in mixed speciality wards; and
- (iv) early discharge of patients to convalescent homes and homes for the elderly, to create new reservoirs of infected and colonised patients (Casewell, 1995).

Local outbreaks of MRSA have been successfully contained through advances in barrier nursing techniques and the presence of specialist infection control nurses. Infection control nurses can act as consultants and local trainers when an MRSA infection or carrier has been identified; they can give local support and advice to nursing staff to ensure spread is minimised.

17. VRE infections are particularly difficult to treat because most causative organisms are also resistant to other commonly-used antibiotics, such as aminoglycosides and ampicillin. VRE bacteraemia is reported in one hospital to lead to 100 per cent in-hospital mortality (Lam et al 1995).

18. The possibility that hospital staff are carriers must be considered, as has been reported recently for ERSA (Back et al, 1993).

19. Hospital pharmacists have a major influence on the use of all medicines in hospital including antibiotics. They often adopt the role of advising and training junior medical staff in the appropriate prescribing of antibiotics and to ensure that local antibiotic policies are followed for the particular infection and patient group. At Leeds General Infirmary, for example, there are written policies in place for (a) general antibiotic prescribing and (b) antibiotic prescribing for surgical patients. A copy is appended, for information.

20. It is pertinent to consider the association between the existence of a sound antibiotic prescribing policy and level of antibiotic resistance in an area. In Finland, with a relatively small population and excellent recording of health data for the whole population, a relationship has recently been established between the reduced prescribing of macrolide antibiotics and a decline in frequency of erythromycin resistance. Responding to the increase in erythromycin resistance which occurred in the 1980s, the Finnish authorities issued national guidelines to recommend a reduction in the use of macrolide antibiotics in treating respiratory and skin infections in outpatients. An educational programme for doctors was instituted and this led to a halving of use from the peak in 1988. The incidence of resistant strains of Group A *Streptococci* that were found in throat swabs and pus samples fell from a peak of 19 per cent resistance in 1990 to 8.6 per cent in 1996 (Seppala et al, 1997).

Recommendation: It is recommended that consideration be given to introducing a similar programme in the UK.

21. There are sound reasons for restricting the use of "second-line" antibiotics and preventing their routine use. The experience of one US hospital is that a programme to restrict vancomycin use is achievable only when operated through the pharmacy department (Belliveau et al, 1996) but a multi-disciplinary approach, with a commitment by all senior hospital staff to the rationalisation process, is required for a successful outcome (Goldman and Huskins, 1997).

22. A strategic approach to the use of antibiotics is essential to avoid the problems posed by the proliferation of antibiotics (Cooke, 1989). At Leeds General Infirmary for example, a co-operative approach between the pharmacy and microbiology departments led to the development of the following objectives:

- to retard the development of microbial resistance and thus prolong the use of well-tried, safe and effective agents;
- to control cross-infection;
- to enable the microbiology laboratory to test for sensitivity to agents currently used within the hospital;
- to promote the informed and effective use of the carefully-selected agents which, by regular use, will become familiar to the prescriber; and
- to reduce the cost by being able to negotiate the bulk reductions from the companies who make the selected agents in view of the guaranteed regular use of the agents.

This approach led to the development of two lists of antibiotics, that is, a primary list of agents based on tried-and-tested compounds having a specific spectrum of activity, and a secondary list of agents that had a restricted use and were only to be employed on the recommendation of the microbiology laboratory or specified specialist.

The outcome of the implementation of these strategies was the total removal of some antibiotics, the rationalisation of the use of cephalosporins, and a decrease in the annual cost of antibiotics. This was achieved without compromising the efficacy, as measured by infection rates in patients undergoing bowel surgery, in whom wound infection rates were unaltered by the change. The period of inpatient stay was reduced during the study period (Graph 1). Table B lists the antibiotics which are included in these two categories. The lists need to be reviewed periodically in the context of the local situation as it relates to bacterial sensitivities. General advice on the selection of antibiotics for specific infections is given in the British National Formulary (copy attached).

23. Hospital central intravenous additive services (CIVAS) have been developed mainly to ensure that patients receive parenteral medicines in a ready-to-use form free from contamination. Many CIVAS services have a useful role in controlling the availability of antibiotics. Pharmacists play an important part in medicines management. Clinical pharmacists assess the suitability of the prescription against antibiotic policy guidelines, ensure that the dose is appropriate for the patient's clinical condition and the diagnosed infection and that the duration of the therapy is appropriate. Consideration is also given to the appropriate switch to the safer and less expensive oral route of administration.

24. Hospital pharmacy departments routinely supply complete courses of antibiotics when patients are seen at Accident and Emergency departments and on discharge from hospital. This is to avoid any break in therapy on moving to the primary care environment to ensure maximum efficacy and the minimum risk of development of resistance. The hospital pharmacist is ideally placed to provide counselling on adherence to dose regimens.

25. Infection Control policies are established by a hospital Infection Control Committee. There is a trend to reduce the use of disinfectants in cleaning procedures, because of environmental considerations and concern about the promotion of resistance. Good cleaning techniques use soap and water. The main use of disinfectants is in the control of cross-infection in hospitals, as part of a general procedure to isolate patients with resistant strains of bacterial infection.

26. The rational use of antibiotics is strongly encouraged by the Royal Pharmaceutical Society. For example, the use of prophylactic antibiotics in invasive procedures has been shown to reduce post-procedural infections such as wound infection after bowel surgery. Prophylaxis usually takes the form of a single dose of antibiotic administered as close as possible to the time of greatest risk of infection, that is, during the time the surgeon is operating and before the wound has been closed. Hospital pharmacists working in surgical units have a major role to play in developing such policies and devising methods to ensure patients receive maximum protection for the relatively short period of maximum risk. This limited exposure effectively reduces infection without promoting antibiotic resistance.

COMMUNITY PHARMACY

27. *Sale and supply of Antimicrobial Agents from Pharmacies.* The Royal Pharmaceutical Society supports the move of medicines from the prescription-only medicines classification to pharmacy-sale where the record of safe use of the product is well established and where there is an indication that the public could self-diagnose with reasonable certainty. There may be sound reasons for some antibiotics to be made available as pharmacy-sale preparations for specific conditions and the case for these changes will be brought forward at the appropriate time.

28. The Royal Pharmaceutical Society supports the move of chloramphenicol eye preparations from a prescription-only medicine to pharmacy-sale status. There is no evidence that chloramphenicol used in eye preparations gives rise to bacterial resistance.

29. The Royal Pharmaceutical Society has submitted evidence to the Department of Health Group under the chairmanship of Dr June Crown which is currently undertaking a review of prescribing, supply and administration of medicines (*Pharmaceutical Journal* 259, 399-403, 1997). The Society has suggested that pharmacists should be able to supply or prescribe medicines in appropriate circumstances to patients who are needing treatment for particular conditions. These medicines, which may include appropriate antibiotics or antimicrobial preparations would be supplied or prescribed by pharmacists.

30. *Advice to patients.* The period of treatment of a bacterial infection with antibiotics is commonly from 5 to ten days, this being the period required to destroy sufficient bacteria to ensure host-mediated eradication of the infection. If the period of treatment is not long enough, or the blood concentrations of antibiotic fall below the level required to kill bacteria for long periods, then the conditions created can lead to the emergence of resistance bacteria. The community pharmacist has an educational role in the use of antibiotics to ensure that the patient understands that:

- (a) every consultation about an infection (such as a sore throat) may not lead to the prescription or supply of an antibiotic;
- (b) there are differences between bacterial and viral infections such that antibiotics are only of use to treat bacterial infections (except where secondary infections in a viral infection are present); and
- (c) the antibiotic must be used properly by taking the medicine in accordance with the stipulated regimen, completing the course of treatment and avoiding potential incompatibilities (with foods and other medicines). Information to patients is supplied both orally and in written form; patient packs contain product information leaflets which explain the dosage regimen in easily-understood terms. A sample of a prescription information leaflet is enclosed.

31. The Royal Pharmaceutical Society supports the introduction into general practice at local level of formularies which provide advice on antibiotic use. In addition, it notes that the selection of antibiotics in the community may be based on susceptibility tests on patients' samples carried out by a local laboratory. The Society believes that the prescribing of antibiotics should take place following a consultation by the patient with a doctor or pharmacist.

32. Those who have the necessary knowledge and experience, including pharmaceutical prescribing advisers, should help and encourage Health Authorities to generate antibiotic policies. Pharmaceutical advisers are well positioned to ensure that the local policies on antibiotic prescribing are fully implemented by producing guidelines for the general medical practitioners, practice nurses and community pharmacists.

INDUSTRY

33. Bacterial resistance to antibiotics and biocides is generally considered as falling into two categories:

- (a) *intrinsic*, a natural property of an organism and usually associated with cell wall and outer membrane permeability; and
- (b) *acquired*, as a result of mutation or by the acquisition of plasmids or transposons.

Recommendation: It is recommended that further research is required in the following areas:

- (i) additional information is needed about the uptake of antibiotic and biocide molecules into MRSA, VRE and MDRTB cells;
- (ii) the role of the mycobacterial cell wall components in conferring intrinsic resistance to antibiotics and biocides needs to be assessed and ways of circumventing impermeability overcome (Russell, 1996);
- (iii) the role of the cell wall as a barrier to the entry of antibacterial agents into MRSA and VRE cells should be evaluated;
- (iv) efflux is now regarded as a major resistance mechanism in MRSA and multiple-drug resistant Gram-negative pathogens (Russell & Chopra, 1996; Levy, 1992; Nikaido, 1994; George, 1996). Analogues of existing drugs that are not recognised by efflux mechanisms need to be developed, such as thiacyclines (Russell & Ahonkhai, 1982) and glycylicylines (Testa et al 1993; Chopra et al, 1997), which are already available, and (for the future) fluoroquinolones and macrolides;

- (v) analogues of existing drugs that are stable to enzymatic inactivation are still needed, such as new β -lactam and new aminoglycosidic antibiotics;
- (vi) newer β -lactamase inhibitors are needed;
- (vii) combined antibiotic therapy and dual-action antibiotic hybrids need to be reassessed;
- (viii) the use of carriers to deliver antibiotics or biocide molecules into bacterial cells must be considered; and
- (ix) alternative targets and strategies should be explored, based on an understanding of microbial behaviour in infection and virulence determinants.

In addition, antibiotic usage must be rationalised and the possible link between antibiotic resistance, biocide resistance and biocide usage must be evaluated (Russell & Chopra, 1996; Russell, 1997).

Finally, it should be noted that as more is learned about resistance mechanisms, it should become possible to utilise these mechanisms as therapeutic targets (Coleman et al 1994).

34. *Specific Diseases.* The Royal Pharmaceutical Society recognises that antimicrobial resistance is a global problem which requires co-ordinated national and international efforts. With this in mind, this Society held two international symposia at its 1996 annual Conference. These addressed Malaria and Tuberculosis.

MALARIA

35. The following were the major points which emerged from the symposium on malaria.

- (i) The problem of drug resistance is a global one and global solutions are required, co-ordinated by the World Health Organisation.
- (ii) There is an urgent requirement for new drugs for the treatment of falciparum malaria; the most serious form of the disease, caused by *Plasmodium falciparum*. Most of the morbidity and over 90 per cent of deaths due to malaria occur in Africa. In most areas, parasite resistance to chloroquine has made this drug ineffective. Many African countries are in the process of changing from chloroquine to pyrimethamine—sulfadoxine as first line treatment of out-patient malaria, although there are already signs in East Africa that pyrimethamine—sulfadoxine will not remain effective for long. The form of resistance designated as R2 to pyrimethamine—sulfadoxine has been reported from Tanzania to Kenya. While there are effective alternative treatments (mefloquine, halofantrine, pyronaridine) these drugs are expensive. African ministries of health will not be able to afford adequate stocks for the treatment of all cases of malaria. Drugs with a long elimination half-life tend to select for parasite resistance rapidly, even when used properly. Drugs with a short half-life, and steep dose-response curves may select less rapidly for resistance. For this reason, new drugs with these characteristics are being sought; the combination of chlorproguanil-dapsone is currently under development as a WHO initiative. Chlorproguanil-dapsone is effective against pyrimethamine-sulfadoxine-resistant parasites, is cheap, and offers an opportunity for operational use while other appropriate treatments are being developed.
- (iii) The use of dosage regimens which promote resistance to anti-malarial compounds is common, particularly in Africa. The normal practice is for villagers in areas where malaria is endemic to self-diagnose malaria when suffering symptoms such as headache or fever. Villagers often self-treat with one or two tablets of an antimalarial preparation, usually chloroquine. Parasitaemia is temporarily reduced, which sometimes allows the patient's immune response to suppress the infection. However, the effect is to select for drug-resistant forms which later recur. In the laboratory setting, exposure to sub-lethal concentrations of chemotherapeutic agents is a classical method for engendering resistance. In the developing countries, the requirement is for better control of medicines and education of the populace (Watkins and Marsh, 1996).
- (iv) Inadequate diagnosis is common in developing countries where many cases of fever arising from other infections are mis-diagnosed as malaria. For accurate diagnosis, it is necessary at the present time to examine stained blood slides. Commonly these facilities are not available. Diagnosis is therefore presumptive and a failure to recover is wrongly attributed to resistance to the antimalarial drug used. This inappropriate medication may then lead to further inappropriate choices, with the drug of first choice by-passed, on the erroneous conclusion of drug resistance. Simpler, cheaper methods of diagnosis of malaria are required (Rollason, 1996).
- (v) Counterfeit medicines are common in the African subcontinent. The use of counterfeit antimalarials (with reduced potency or devoid of active ingredient) can lead to the development of resistance, or the incorrect diagnosis of drug resistance, respectively.

TUBERCULOSIS

36. One issue of importance in pharmacy is the reported potential for poor or impaired systemic absorption of rifampicin from combination products (with isoniazid and pyrazinamide) used in the initial phase of treatment, as reported by Fox (1990). This is of sufficient importance for the World Health

Organisation to organise a programme of licensing of third world manufacturers who are making these combination products. Pharmacists also have a role in encouraging adherence with dose regimens which, typically, last for six months or longer. The community pharmacist has a role in identifying possible cases of tuberculosis in the community, by referral to a general medical practitioner of anyone who has a persistent cough of three or more weeks duration.

37. The emergence of multi-drug-resistant tuberculosis is a cause for concern. The (US) National Action Plan to Combat MDR-TB is outlined by Villarino et al (1992). The Chief Administrative Pharmaceutical Officer of Lothian Health has been approached to develop a community pharmacist led supervised antitubercular self-administration service, similar to that developed for methadone in drug users to ensure good compliance. The prevention of resistance is dependent on adherence with dosage regimens. It is here that the concept of concordance comes into play and a therapeutic alliance is forged, with a shared understanding of the importance and relevance of the treatment. The eradication of tuberculosis is a major public health issue.

REFERENCES

- Alqurashi, AM, Day MJ and Russell AM (1996) *J Antimicrob Chemother* 38, 745.
- Anderson RL, Carr JH, Bond WW and Favero MS (1997) *Infect Cont Hosp Epidem* 18, 195-199.
- Arthur M, Reynolds PE et al (1996) *J Infect* 32, 11-16.
- Back, NA et al (1993) *JAMA* 270, 1329.
- Barry EC III and Mdluli K (1996) *Trends Microbial* 4, 275-281.
- Belliveau PP et al (1996) *Am J Health-System Pharm* 53, 1570.
- Casewell MW (1995) *J Hosp Inf* 30 Suppl, 465.
- Chopra I, Hodgson J, Metcalf B and Postle G (1997) *Antimicrob Ag Chemother*. 41, 497-503.
- Coleman K, Athalye KM et al (1994) *J Antimicrob Chemother* 33, 1091-1116.
- Cooke J "The Role and Function of the Community and Hospital Pharmacist in the Health Care Systems in Europe" *WHO Working Group Report* (1989) Styx Publications, Groningen ISBN 90-72371-06-2.
- Cookson BD, Bolton MC and Platt JH (1991) *Antimicrob Ag Chemother* 35, 1997-2002.
- Courvalin P (1996) *J Antimicrob Chemother* 37, 855-869.
- Fox W (1990) *Tubercle* 71, 241.
- George AM (1996) *FEMS Microbial Lett* 139, 1-10.
- Goldman DA and Huskins WC (1997) *Clin Inf Dis* 24 Suppl 1 S139.
- Griffiths PA, Babb JR, Bradley CR and Fraise AP (1997) *J Appl Microbial* 82, 519-526.
- Grüneberg RN (1994) *J Antimicrob Chemother* 33 Suppl A, 1-8.
- Hackbarth CJ and Chambers HF (1989) *Antimicrob Ag Chemother* 33, 991-994.
- Inderlied CB, Kempner CA and Bermulez L E M (1993) *Clin Microbial Res* 6, 266-310.
- Jarlier V and Nikaïdo H (1990) *J Bacteriol* 172, 1418-1423.
- Lam S et al (1995) *Am J Inf Control* 23 170.
- Levy SB (1992) *Antimicrob Ag Chemother* 36, 695-703.
- Littlejohn TG, Paulsen IT et al (1992) *FEMS Microbial Lett* 95, 259-266.
- Lyon BR and Skurray RA (1987) *Microbial Rev* 51, 88-134.
- Nikaïdo H, Kim S-H and Rosenberg EY (1993) *Mol Microbial* 8, 1025-1030.
- Nikaïdo H (1994) *Science* 264, 382-388.
- Paulsen T, Brown MH et al (1996a) *Proc Natl Acad Sci USA* 93, 3630-3635.
- Paulsen IT, Skurray RA et al (1996b) *Mol Microbiol* 19, 1167-1175.
- Rollason PV (1996) *J Pharm Pharmac* 49 Suppl 2, 13.
- Russell AD (1996) *J Appl Bacteriol Symp Suppl* 81, 87S-101S.
- Russell AD (1997) *J Appl Microbial* 82, 155-165.
- Russell AD and Ahonkhai I (1982) *J Antimicrob Chemother* 9, 445-449.
- Russell AD and Chopra (1996) *Understanding Antibacterial Action and Resistance*, 2nd edition. Ellis Horwood, Chichester.
- Seppala H et al (1997) *New Engl J Med* 337, 441.
- Speller et al (1997) *Lancet* 350, 323-325.

Stickler DJ and King BJ (1992) In *Principles and Practice of Disinfection, Preservation and Sterilization* (eds Russell AD, Hugo, WB and Ayliffe GAJ), 2nd edn, pp 211-224. Blackwell Science, Oxford.

Tenover FC and McGowen JE, Jr (1996) *Am J Med Sci* 311, 9-16.

Testa RT, Petersen P *et al* (1993) *Antimicrob Ag Chemother* 37, 2270-2277.

Titcomb L (1997) *Pharm J* 258 28.

van Kingeren B and Pullen W (1993) *J Hosp Infect* 25, 147-149.

Villarino ME *et al* (1992) *Public Health Reports* 107, 616.

Watkins WM and Marsh KJ (1996) *J Pharm Pharmac* 49 Suppl 2, 13.

Williams JD, Bergen T and Moosdeen F (1997) *Newsletter In Soc Chemother* 1, 1.

World Health Organisation (1996) *Treatment of Tuberculosis. Guidelines for National Programmes*. WHO, Geneva.

Zhang Y and Young D (1993) *Trends Microbiol* 1, 109-113.

Zhang Y and Young D (1994) *J Antimicrob Chemother* 34, 313-319.

SUMMARY OF RECOMMENDATIONS

In relation to *Mycobacteria*, it is recommended that:

- (i) further research be undertaken on cell wall components involved in resistance to antibiotics and biocides;
- (ii) further research be conducted on how drugs are transported across cell walls;
- (iii) reasons for the high resistance of *M. chelonae* to glutaraldehyde be sought. (iv) improved and faster methods for testing for mycobacterial sensitivity are developed; and
- (iv) improved and faster methods for testing for mycobacterial sensitivity are developed.

In relation to *MRSA*, it is recommended that:

- (i) monitoring of the emergence of vancomycin-resistant *MRSA* be undertaken as a matter of urgency; and
- (ii) studies be carried out to determine whether low concentrations of biocides can select for the survival of antibiotic-resistant *Staphylococci*.

In relation to *VRE*, it is recommended that:

- (i) uptake of drugs and biocides into *VRE* be investigated;
- (ii) the reasons for the greater efficacy of teicoplanin, compared to vancomycin, against vanB and vanC phenotypes be studied; and
- (iii) that teicoplanin analogues whose binding is unaffected by D-Ala-D-Lac be produced.

In relation to *multidrug resistant Gram-negative bacteria*, it is recommended that:

the effects of biocides on multiple antibiotic-resistant strains be studied.

In relation to the *possible linked antibiotic-biocide resistance*, it is recommended that:

- (i) there is an urgent need to provide information about the bactericidal, as opposed to bacteriostatic, activity of chlorhexidine, quaternary ammonium compounds and other biocides on *MRSA* and *MRSE* possessing *qac* genes;
- (ii) activity of biocides against multidrug resistant Gram-negative bacteria, where multi-drug efflux exporters are responsible for resistance, should also be examined critically;
- (iii) suitable new disinfection policies may have to be produced and the usage of skin antiseptics reviewed; and
- (iv) the clinical relevance of a possible association between antibiotic resistance and biocide resistance be assessed forthwith.

In relation to the *monitoring of resistance*, it is recommended that:

monitoring systems to record the pattern of antibiotic usage are in place.

In relation to the *reduction in the prescribing of macrolide antibiotics* achieved in Finland, it is recommended that:

consideration be given to instituting a similar programme in the UK.

In relation to the *research to be conducted in industry*, it is recommended that:

this be conducted in the eight areas identified in Section 33.

Table A

INCREASE IN THE NUMBER OF ANTIMICROBIAL AGENTS INCLUDED IN THE BRITISH NATIONAL FORMULARY (ADAPTED FROM COOKE, 1989).

	1968	1978	1988	1997
Penicillins	6	10	25	14
Cephalosporins	1	3	14	16
Aminoglycosides	4	4	7	6
Others	15	14	33	44
Total	26	31	79	80

Table B

ANTIBIOTICS: PRIMARY AND SECONDARY AGENTS

1. *A primary list of agents based on tried and tested compounds having a specific spectrum of activity:*

Benzylpenicillin and phenoxymethylpenicillin for the treatment of infections caused by organisms such as *Streptococcus viridans* and *Streptococcus pneumoniae*;

Cloxacillin for the treatment of penicillinase-producing *Staphylococcus aureus* infections;

Ampicillin for the treatment of respiratory infections due to *Haemophilus influenzae* and *Streptococcus pneumoniae* and for systemic infections due to *Streptococcus faecalis*;

Erythromycin for the treatment of respiratory infections as above and for atypical pneumonias due to *Legionella* and *Mycoplasma*;

Trimethoprim for the treatment of urinary tract infections (usually coliform organisms);

Cephadrine alone or in combination with metronidazole for prophylactic use in surgery;

Metronidazole for anaerobic infections;

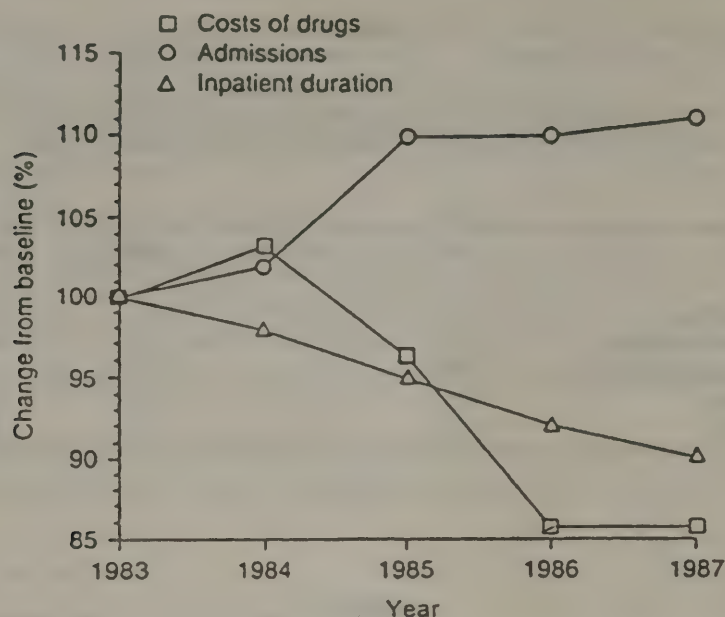
Gentamicin for the treatment of serious sepsis due to gram-negative organisms.

2. *A secondary list of agents that had a restricted use and were only to be employed on the recommendation of the microbiology laboratory or designated specialists:*

Agents on this secondary list included, for example, aztreonam, cefotaxime, chloramphenicol and ciprofloxacin.

Piperacillin was reserved for use, in combination with gentamicin, for the treatment of neutropenic patients with febrile episodes.

Vancomycin was reserved for the treatment of sub-acute bacterial endocarditis infections due to streptococcal or staphylococcal organisms when patients are allergic to penicillins. It was also reserved for the treatment of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis and for patients with infections due to *Staphylococcus epidermidis* (*albus*). These are usually patients who have developed a bacteraemia in association with a prosthetic device or indwelling cannula.



Graph 1. Percentage changes in costs for antimicrobial agents, duration of inpatient stay and number of admissions to Leeds General Infirmary, Leeds, England, after the introduction of formulary guidelines for the use of antimicrobial agents. Changes are relative to baseline measures taken before the introduction of guidelines in 1983.

Memorandum by The Royal Society

This submission was prepared by a group of Fellows chaired by Professor P J Lachmann Sec RS. The other members were Sir John Skehel, FRS and Professor B G Spratt FRS. It has been endorsed by the Council of the Royal Society.

1. We have considered the Committee's questions and offer the following comments.
2. We would like to stress the international nature of the issues under consideration and emphasise that effective solutions will not be achieved by the UK acting alone. Drug resistant organisms do not respect national boundaries and with the ease and rapidity of modern travel infections can be transported far from their origins very quickly.
3. The main reason for the current unsatisfactory situation is that, worldwide, there is no effective regulation of the use of antibiotics. In many nations drugs are freely available "over the counter" and even in countries where most drugs are only available on prescription there may be little control. The practice in some societies of doctors prescribing the most potent drug available—just in case—may be leading to resistance to drugs which for some infections are the final barrier before they become untreatable.
4. To try to remedy this situation before the complete arsenal of antibiotics is exhausted will require regulation, enforceable internationally. The regulation should include the following features:
 - the availability of new drugs must be more effectively controlled than hitherto;
 - the sale of drugs over the counter must be curtailed;
 - the practice of prescribing the strongest drug without justification must be discouraged;
 - the practice of not prescribing antibiotics for non-life threatening infections unless samples grown in culture are shown to respond to them should be encouraged; and
 - the introduction of any new classes of antibiotics, particularly those that are the sole effective treatment of infections, must be very carefully regulated.
5. We recognise the difficulty in implementing the above but there are already strains of enterococci and *Mycobacterium tuberculosis* that are resistant to all of the major classes of antibiotics and we believe that there is a likelihood that some strains of additional pathogens may soon become untreatable. Thus the need for research and development of new drugs is urgent.
6. Drugs of several classes are required. If only one new class became available its likely overuse (in consequence of the lack of other effective treatments) would still leave open the prospect of resistance to it developing rapidly.
7. We recommend the vigorous encouragement of research to discover and develop new classes of antibiotics. In addition to natural product antibiotics we would encourage attempts to discover novel

antibiotics, for example via development in combinatorial biosynthesis and synthetic chemistry. We would encourage research into the assessment of new targets for antimicrobial agents.

8. Development of effective vaccines for common childhood bacterial and viral infections would be particularly useful in reducing the worrying overuse of antibiotics in children.

9. Most of what we have said thus far pertains to bacterial disease. The problems with viral disease are due more to the dearth of effective chemical treatments than, as yet, to resistance, though there are some successful examples notably acyclovir against herpes. Vaccines have been developed against many viruses and the main hope for combating such scourges as HIV also rests in the development of vaccines.

10. Similarly, the increasing chemoresistance observable in malaria infections, and the lack of any prospect of new antimalarials being available soon, suggest that the best hope for the future lies with developing suitable vaccines. Research in this area is also urgently needed as the disease is taking hold ever more strongly in areas where it had previously been easily treatable and, because of human migration and climate change, may continue to expand its range to embrace susceptible populations in areas that were not previously under threat.

11. However, the development of vaccines, especially live attenuated vaccines, has not been an attractive prospect for the pharmaceutical industry because of the possibility of insufficient return on the costs of development. The public both in the UK and elsewhere are, quite reasonably, averse to risk and as a result major trials of potential vaccines are required before they can be widely used. The development of resistance has reached such a serious stage that perhaps the question should now be asked whether the degree of risk that is deemed to be acceptable should be re-examined and safety-testing regimes simplified in order to allow products to reach the market faster.

12. We note that the terms of reference of the Inquiry do not include the use of antibiotics as growth promoters, and for prophylactic and therapeutic purposes, in animals and fish, nor the use of antibiotic resistant markers in genetically modified organisms, but welcome the fact that they are being considered by the relevant Government Advisory Committees.

13. Finally one important aspect of the development of bacterial disease resistant strains is the potentially very high cost of containment if they take hold in hospitals or other public institutions. Many of those resident in the UK will not recall the spectre of isolation hospitals for tuberculosis patients, but having to resurrect the concept on a large scale to deal with a resistant epidemic of TB (a situation that already exists elsewhere in the world) is not beyond the realms of possibility. Therefore, one further recommendation we would make would be for the urgent development of a strategy to deal with patients infected with drug-resistant TB and untreatable vancomycin-resistant MRSA. This strategy will need to address difficult questions about confinement and monitoring of patients.

17 December 1997

Memorandum from the Department of Medical Microbiology, St. George's Hospital Medical School

Widespread use of antimicrobial agents throughout the world will inevitably lead to resistance to these agents. The end result is a patient with an infection, such as tuberculosis, which is resistant to many antimicrobial agents, costs over £100,000 a year to treat and often leads to death. This submission deals with areas which, if improved, will help to counteract the recent rise in antimicrobial resistance, particularly multi-drug resistant tuberculosis (MDRTB).

We have data concerning our experience of MDRTB which leads us to believe that significant factors in the emergence of resistance are the ethnic origin of the patient and poor compliance with therapy. We are happy to provide the Committee with details if it wishes.

1. Full supervision of drug taking; this method is effective in improving compliance, but requires increased resources.

2. New drugs:

- (a) A clinical mycobacterial MRC unit with long-term funding is needed to perform the necessary research which is required to underpin drug development. Tasks of this unit should include preclinical drug-testing, animal models, clinical trials, epidemiology and social aspects.
- (b) An Orphan drugs Programme
- (c) Pharmaceutical industry: government should introduce incentives for industry to develop new drugs.
- (d) Basic Research: Increased investment in basic antimicrobial research offers the only hope of a long-term solution to the rise in resistance. Avenues of research which are likely to yield favourable results include the identification of new drug targets, development of strategies that kill stationary phase organisms which are phenotypically resistant to virtually all known antimicrobials, identification of novel natural mechanisms of resistance and new vaccines.

3. *Hospital facilities for management of tuberculosis.* It is vital that the clinical and laboratory facilities for management of patients with tuberculosis combine to receive appropriate support. These represent the "front-line" of defence against multidrug resistance and they require the expertise to apply containment and

treatment policies effectively. The existing policy of funding needs modifying to prevent large-scale removal of funds from Medical Microbiology Departments. Rapid culture of the organisms, and early elucidation of its sensitivity to antimicrobial agents is vital to the correct management of infected patients and may prevent the emergence of broad spectrum resistance in organisms initially resistant to only one agent. The huge majority of sensitivity tests are performed by Hospital Medical Microbiology departments. However, in the case of *Mycobacterium tuberculosis*, sensitivity tests are performed centrally. Whilst this practice is satisfactory when MDRTB was very rare, in the present situation for hospitals with an increasing resistance problem, the tests should be done locally. This will make the service more responsive and faster for the clinicians and will eliminate the delay, communication problems and transport costs of the off-site service.

4. Long-term care of MDRT patients. The Sub-Committee should be made aware of the inhumane nature of the present arrangements.

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Chairman of Department,
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Consultant in Infectious Diseases

Dr C. Rayner
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23 September 1997

Memorandum by the Scottish Microbiology Association (SMA)

1. While it is technically true to say that there is no absolute proof of a causative association between antibiotic use and resistance, many authorities believe the association to be "virtually certain"¹. With this and the impossibility of controlling for all compounding factors in prospective trials, a pragmatic approach to the control of antimicrobial resistance is essential. Given the recent escalation in resistance and the overwhelming evidence of much over-use of antibiotics (and thus unnecessary resistance) the pragmatic and essential approach is to act now to control antibiotic use. The important question is how, not whether. Much research is still needed in this area and to a large extent local problems probably are best addressed by local solutions. However there has been no shortage of National Guidelines on this topic both in the UK² and USA³. The recent Strategic Goals statement from the USA³ may be a step in the right direction but will need modifying for different countries. A recent meeting in Scotland has started to address this issue. Better diagnostic and therapeutic protocols are also likely to be important, perhaps incorporated as Scottish Intercollegiate Guideline Network (SIGN) guidelines. The EC and the European Society for Clinical Microbiology & Infectious Diseases (ESCMID) are addressing these issues although currently there is no UK initiative due to funding.

CURRENT ACTIVITIES

2. The Scottish Microbiology Association (SMA) through its Scottish Antimicrobial Resistance Surveillance (SARS) group has been trying to set up a national resistance surveillance system for the past two years with pilot funding from the Scottish Office but the application has been rejected on two occasions, latterly on the grounds that this is a "service development". Currently, small projects are progressing piecemeal with pharmaceutical sponsorship.

3. The SMA was invited by the Scottish Centre for Infection and Environmental Health (SCIEH) to join a Working Group to address the question of routine reporting of Target and Alert organisms through SCIEH's Weekly Report. Despite agreement on these lists we have been waiting over a year for their implementation.

4. Through its contacts with other Celtic associations (The Welsh and Irish) the SMA has been addressing Hospital Acquired Infection (HAI) and Antibiotic Resistance Surveillance (ARS) on a collaborative basis. The conclusion was that Lotus Notes was the best way of communicating between laboratories with Formic software but the Scottish Office is progressing with a less satisfactory system (COSURV).

5. With the encouragement of the SMA, the Scottish Office has set up a committee to look at HAI. At the moment this has no brief to look at ARS although both this committee and the SMA have been in touch with the British Society for Antimicrobial Chemotherapy (BSAC) and the Public Health Laboratory Service (PHLS) about linked surveillance.

6. The Chairman of the SARS Group has put proposals to both the BSAC and Hospital Infection Society (HIS), over the past three years, to form Working Parties on antibiotic control in hospitals (the most pressing area for future control measures) but both proposals have been turned down, as was one to (SIGN).

7. A second application to SIGN has been submitted, proposing to create guidelines on Surgical Antibiotic Prophylaxis and also on Diagnosis and Empiric Treatment of Sepsis. Future bids are planned to the Scottish Office for Audit and Research money. Results of a SMA/Eastern Europe bid to the EC for funding for ARS, Europe-wide, are awaited.

HOSPITAL USE

8. Very little data on hospital antibiotic use in the UK has been published, although much must be available, relatively easily, on amounts of prescribing, through computerised pharmacy systems⁴. It is probable that prescribing continues to escalate both in amount and costs throughout the country. Unfortunately, until computerised prescribing is developed, we have relatively little data on quality of prescribing. The little data we have (from very labour intensive audits) suggests much room for improvement⁵. However, in terms of antibiotic misuse and resistance rates, the UK is somewhere between N Europe (both very low) and S Europe (both very high). Thus, particularly amongst clinicians and administrators, the size/importance/relevance of the problem in the UK is not grasped. Cost saving probably drives most antibiotic control measures at the moment. Spread of resistance is facilitated by poor isolation facilities, lower bed numbers, patient boarding, staff shortages (including relatively few infection control nurses and a decreasing number of "on the ward" consultant microbiologists due to laboratory mergers), lack of laboratory resources, lack of surveillance and lack of appropriate specimen collection and result feedback. Calmanisation has also had a deleterious effect in terms of continuity of care.

9. The reasons for increasing use and abuse of antibiotics in hospital are likely to be complex. Undoubtedly, some increased antibiotic use is appropriate with the increased burden of immunosuppressed patients and more heroic therapeutic measures. However, the increased pressure to discharge patients as soon as possible may have led to more therapeutic empiricism. Antibiotic resistance itself starts a vicious circle with use of newer, more expensive agents creating further rises in resistance to these new agents. More evidence can be provided on request.

GENERAL PRACTICE USE

10. Very little data is available on this although recent publications^{6,7,8} and locally available data suggest a large and increasing amount of (inappropriate) prescribing. The tendency is to treat empirically without any laboratory investigation and this must have been encouraged by the last government's Health Service Reforms, with their introduction of charging for laboratory use. Similarly, there are no incentives to take time to investigate patients for evidence of bacterial infection prior to antibiotic prescription. While cross infection magnifies antibiotic resistance problems in hospitals, the vastly greater amount of antibiotic prescribing in General Practice suggests this is also an important area for increased efforts. Improvements will, however, require changes in work schedules.

11. Grampian is one of few Health Boards/Authorities with a linked GP/hospital antibiotic policy. Whether this helps promote good quality prescribing is conjectural but we feel probable. There is a high concordance of prescribing with the policy recommendations and antibiotic sensitivities reported to GPs include only formulary antibiotics. However, in common with all policies, the emphasis is on "what" to prescribe rather than "when not" to prescribe. The recent papers from McFarlane *et al* in the BMJ^{7,8} confirm previous work showing a high level of inappropriate prescribing in general practice with little appropriate use of the laboratory.

FUTURE DIRECTIONS

12. Clearly, much more research on prescribing and improved surveillance are essential. It must be made easier to obtain funding for these projects, preferably with a national policy for each, with a view to integrated surveillance with good feedback to prescribers and good studies to establish the best intervention methods to improve quality of prescribing in hospitals and the community (and in veterinary practice/animal husbandry). Behaviour and educational psychologists may have a role to play in teaching us how to educate prescribers to change their irrational prescribing habits. Patient education is also being tried. In Holland limits are put on prescribing budgets. Consequently they have the lowest prescribing rates in the world (and the lowest resistant rates). Outcome data, while scarce, do not show any evidence of poor clinical performance. Education of GPs, possibly with incentives, to use the laboratory appropriately for diagnosis of infections is a priority⁹ and will be all the more important if GP prescribing budgets are to be capped. Improved communication between the laboratory and prescribers can ensure more evidence based prescribing¹⁰. Increasing audit resources will allow better definition of the problems, allowing improvements to be implemented. Finally, the subject is given inadequate time at medical school.

REFERENCES

- 1 SHEA Position Paper. (1997) Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the prevention of antimicrobial resistance: Guidelines for the prevention of antimicrobial resistance in hospitals. *Infection Control and Hospital Epidemiology* 18 275-291.
- 2 Working Party of the British Society for Antimicrobial Chemotherapy. (1994) Hospital antibiotic control measures in the UK. *Journal of Antimicrobial Chemotherapy* 34 21-42.
- 3 Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP *et al* (1996). Strategies

- to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. *Journal of American Microbiology Association* 275 234-240.
- 4 Gould IM & Jappy B (1996) Trends of hospital antibiotic prescribing after introduction of an antibiotic policy. *Journal of Antimicrobial Chemotherapy* 38 895-904.
 - 5 Gould, IM (1996) Hospital antibiotic use and its control—The UK experience, In *Du Bon Usage Des Antibiotiques À L'Hôpital* Eds: M Wolff, AC Crémieux, C Carbon, F Vachon, JP Coulaud, JL Vildé. Publ. Arnette Blackwell.
 - 6 Davey PG, Bax RP, Newey J, Reeves D, Rutherford D, Slack R, Warren RE, Watt B, Wilson J (1996) Growth in the use of antibiotics in the community in England and Scotland in 1980-93. *British Medical Journal* 312 613.
 - 7 MacFarlane J, Prewett J, Rose D, Gard P, Cunningham R, Saikku P, Euden S & Myint S (1997) Prospective case-control study of role of infection in patients who reconsult after initial antibiotic treatment for lower respiratory tract infection in primary care. *British Medical Journal* 315 1206-1210.
 - 8 MacFarlane J, Holmes W, MacFarlane R & Britten, N (1997) Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *British Medical Journal* 315 1211-1214.
 - 9 Shackley P, Cairns J & Gould IM (1997) Accelerated bacteriological evaluation in the management of lower respiratory tract infection in general practice. *Journal of Antimicrobial Chemotherapy* 39 663-666.
 - 10 Burke JP & Pestonik SL (1996) Breaking the chain of antibiotic resistance. *Current Opinion in Infectious Diseases* 9 253-255.

Memorandum by SmithKline Beecham Pharmaceuticals

PART A ANTIBACTERIALS

1. INDUSTRY EFFORT IN THE DEVELOPMENT OF NEW ANTIBIOTICS

1.1 *Historical Perspective*

The period between 1945 and 1970 has been described as the "golden age" of antibiotic discovery. Large scale screening programmes for new antibiotics within the pharmaceutical industry resulted in the discovery of virtually all the current, structurally diverse, antibiotic classes with clinical utility. Indeed, based on the perceived potential for these drugs, by the end of the 1960's it was widely believed that bacterial infection would soon be conquered. This apparent success in infection control caused a number of pharmaceutical companies to reduce their antibacterial research effort in favour of alternative infectious disease areas (antivirals/antifungals) or indeed in favour of unrelated therapeutic areas. Some even exited the field entirely.

Those companies that continued antibacterial research have faced technological and commercial barriers to the discovery of new drugs and it is a fact that no new chemical classes of antibiotic (defined as acting on a new bacterial molecular target) have been commercialised in the last 25 years. The traditional, semi-empiric approaches of chemical modification of known antibiotic classes and the search for new structures *via* natural product screening programmes have yielded progressively fewer development candidates. More often than not, the compounds identified could not be progressed on commercial grounds because their advantages over existing, increasingly generic, antibiotics were largely incremental and not sufficient to justify the development costs. The effect this has had on the recent availability of new antibacterial drugs can be seen in certain published data. For example, the FDA reported that the number of commercial INDs (Investigational New Drugs) for anti-infective drug products (excluding antivirals) has fallen steeply in recent years (59 in 1993, 19 in 1994, 22 in 1994 and only 12 in 1996). INDs for all other therapeutic areas (including antivirals) either remained constant or increased. A comparison of the NME's (New Medical Entities) in the pipelines of the top 15 pharmaceutical companies in 1996 with historical marketing data was undertaken by the Centre for Medicines Research. This also reveals an apparent decline in the development of new anti-infective drugs relative to other therapeutic areas.

In the absence of any major new antibacterial drug classes, bacterial resistance to marketed drugs, particularly among Gram positive bacteria, has been increasing alarmingly. Furthermore, the ability of bacteria to become resistant to multiple combinations of antibiotics (the "superbug" scenario) argues against widespread community use of combination therapy except for certain clearly defined infections (eg TB).

Multiple antibiotic-resistant bacteria are now commonplace and of great concern. For example, some enterococci isolated from wound infections are now resistant to all existing drugs and our reliance on vancomycin, as the last remaining agent for treating methicillin-resistant *Staphylococcus aureus* (MRSA), is seriously threatened by the recent discovery of isolates from both Japan and the USA with reduced susceptibility to the drug. Perhaps of greater concern are the increasing number of isolates of *Streptococcus pneumoniae*, the most common cause of pneumonia, now resistant to most beta-lactam and macrolide

antibiotics which are the first-line drugs used for treating this disease. Moreover, the spread of strains from the hospital ward to the community setting is also occurring with increasing frequency. This is likely to be associated with moves to release patients from hospital earlier to complete therapy at home, an untoward trend evident in both Europe and the USA. Other bacterial pathogens in which resistance to available therapies is giving increasing cause for concern include *Mycobacterium* spp, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Shigella dysenteriae*, *Pseudomonas aeruginosa* and *Bacteroides* spp.

However, this situation may change for the following reasons. First, a greater awareness of the increasing problem of bacterial resistance has led to renewed support in the commercial sector of pharmaceutical companies to discover new agents effective in the treatment of bacterial disease. Secondly, this has happened during a renaissance in both biological and chemical sciences, driven principally by the revolutions in genomics and medicinal chemistry. The pharmaceutical industry is, technologically, in a state of transition; a period in which both traditional and new (genomics-based) approaches are being applied to antibiotic discovery.

1.2 Prospects in the short term

In the short term, traditional methods are being used ever more vigorously to identify opportunities which may have been overlooked or not pursued in the past. It should be recognised that, despite the discovery of well over 20 structurally, and mechanistically, diverse classes of antibacterials, only five of these (beta-lactams, macrolides, fluoroquinolones, aminoglycosides and now, glycopeptides) are used widely in medicine. The remainder have been either (a) used sparingly because resistance is known to readily arise during therapy (eg rifamycins), (b) restricted to topical use because of systemic metabolism (eg mupirocin), (c) restricted to veterinary use (eg streptogramins, pleuromutilins) or (d) not used because of unacceptable side effect profile.

Examples of near term products based on previously identified antibiotics include:

- Synercid, a synergistic combination of two antibiotics, has proved effective in Phase 3 clinical trials against infections caused by MRSA and antibiotic-resistant strains of *Enterococcus faecium*. This drug, related to Virginiamycin, an existing streptogramin veterinary product, will require parenteral administration but promises to be valuable in the treatment of serious infections in hospitalised patients.
- New quinolone antibiotics such as grepafloxacin and trovafloxacin are also in Phase 3 development. These possess improved activity against *S. pneumoniae*, including strains resistant to most beta-lactams and all macrolides, are well absorbed orally and require only once-daily administration. It is anticipated that such compounds will play a significant role in the treatment of community acquired respiratory infections—at least until the prevalence of isolates already resistant increases.

Further behind in development (Phase 1/2) are a number of other antibiotics including a novel glycopeptide active against vancomycin-resistant bacteria, even more potent fluoroquinolones such as SmithKline Beecham's SB 265805 and two compounds, linelozid and everninomycin, which have distinct mechanisms of action. The latter compound represents an example of a compound discovered during the "golden age" but set aside at the time. These antibiotics, being earlier in the development process, still have a number of development hurdles to be overcome and their future commercialisation and clinical utility is less certain.

1.3 Future developments

In the longer term, the relentless progress of science and technology is likely to breach the previous barriers to the discovery of new and structurally diverse methods of infection therapy, prophylaxis and diagnosis.

1.3.1 Bacterial genomics and new molecular microbial targets for antibiotic action

The paucity of new molecular targets used to screen diverse series of chemicals for appropriate biological activity was the first barrier to antibiotic discovery. Bacterial genomes are comparatively small (between 0.6 and 6Mb) and since a high proportion of their DNA sequence encodes gene products, it is now both feasible and effective to sequence entire bacterial genomes. Their small size, coupled with the ability rapidly to test the functional importance of candidate molecular targets to microbial survival by disruption of the corresponding genes, ensures that modern molecular microbiology will spearhead the social and clinical impact of the genomics revolution.

This revolution in bacterial genomics, which has been funded predominately by commercial institutions, has already identified many new molecular targets for therapeutic intervention. This is expected to result in a significant number of new antibacterial compounds entering clinical development within three years.

SmithKline Beecham has led the pharmaceutical industry in this area. Beginning in 1994 (more than a year before the publication of the first complete bacterial genome) we, and subsequently other pharmaceutical companies, have invested several £millions in genome sequencing and bioinformatics to identify new ways of treating bacterial disease. The importance and the high cost of this approach is emphasised by the fact that the two premier UK-based international pharmaceutical companies (SmithKline Beecham and Glaxo

Wellcome) are collaborating in a joint venture to sequence the genomes of a number of key bacterial pathogens. This collaboration also provided an opportunity to help fund academic bacterial sequencing projects (*Escherichia coli* and *Chlamydia trachomatis*). Microbial genome sequencing capability worldwide has since expanded explosively and there are currently over 50 bacterial genome sequencing projects underway.

Bacterial genome sequences, correctly assembled and annotated, obviously contain all therapeutic molecular targets associated with the pathogens themselves. The challenge is to identify them. SmithKline Beecham, among a limited number of other pharmaceutical companies, have invested heavily in the development of suitable technologies, both in house and in collaboration with academia. A genome size of 2.8Mb (eg *S.aureus*) contains ~2,000 genes of which ~10 per cent (200) may be essential for bacterial growth *in vitro*. The proportion of such genes common to a range of different pathogens is not yet known but if new antibiotics are successfully developed that interact with the gene products of only 5 per cent of the 200 such potential molecular targets, this would represent 10 new antibiotic classes. This would more than double the current number of classes of widely used anti-infectives.

The identification of new molecular targets from bacterial genomes not only facilitates the discovery of new antibiotic classes to combat the rising tide of bacterial resistance, but also offers the exciting prospect of discovering new types of therapies that act by modulation of pathogen adaptation/survival strategies within their mammalian hosts. Such compounds may significantly improve the prospects of treating severely immunocompromised patients or those suffering from chronic infections. Current treatment regimes for these patients is frequently difficult and protracted, necessitating (at best) prolonged hospitalisation—with all its associated costs. In this way, we may expand the horizons for anti-infective therapy beyond the confines of agents that are merely bacteriocidal or bacteriostatic.

1.3.2 Chemical diversity

One of the reasons why the golden age of antibiotics came to an end was the exhaustion of the supply of new chemicals to screen for antimicrobial activity.

The lack of chemical diversity is being addressed via a revolution in medicinal chemistry based on the use of combinatorial methods of molecular synthesis to generate very large “libraries” of diverse chemical structures. The changes being implemented are as far reaching as the adoption of mass production techniques were to the automobile industry. Instead of medicinal chemists each synthesising target compounds via a complex set of individual reactions, robotic solid phase systems are being developed to make libraries of compounds which cover virtually the entire range of chemico-physico parameters achievable. The output of compounds per chemist has risen from 25–30 per year to $\geq 10,000$. In addition, there is an expanding area of research to derive diversity from natural sources using new technologies. Specifically, the use of recombinant DNA technology to increase diversity through genetic engineering and through expressing biochemical pathways from micro-organisms that cannot be cultivated *in vitro*.

1.3.3 Capacity of screening programmes

A possible third barrier, which could have become evident with the demolition of the above two, relates to the potential problem of limited screening capacity. However, extensive investment by the industry has led to a new wave of screening technologies. As a consequence, screening capacity within many industrial research institutes has increased from a few hundred to around 20,000 assays per day and in two years time, a throughput of up to 200,000 compounds per day will be achievable. This is expected to cope with the increased numbers of compounds and screens currently being made available.

1.3.4 Investment vs restrictions

The opportunities afforded by new technologies are legion. To match these, antibacterial research within SmithKline Beecham has recently been awarded special status with the establishment of a new research initiative, “Manhattan Micro”. This name was chosen for its connotations to the “Manhattan Project” at Los Alamos that led to the successful development of the atomic bomb during the Second World War. The urgency of the situation is viewed as comparable in that society is expected to face a “vulnerability window” between 2000–2007 in which multi-resistant organisms will increase in clinical importance without parallel progress in the introduction of new antibiotic classes. It signifies the intense, multidisciplinary effort and resource being dedicated to antibacterial research and is unique within the company in that it has dedicated genomic, bioinformatic, molecular genetic, microbiological, alliance management and legal resources allocated to pursue the discovery of new antibacterial agents with utmost vigour.

However, the industry’s success in realising this potential is dependent, to a large extent, on the commercial and regulatory framework within which the pharmaceutical industry operates. Clearly, for pharmaceutical companies to succeed in a highly competitive environment, the allocation of discovery and development resources has to be geared towards products of clear commercial potential, irrespective of therapeutic area and the legislative climate has to recognise the critical role of patent protection on novel inventions.

Given that the total R&D cost of taking a compound to market is now considered to be \$600 million (£375 million), compelling intellectual property protection and the availability of a sufficient period of market exclusivity to generate meaningful commercial returns will continue to be a key factor in future antibacterial discovery initiatives. Inappropriate restrictions which threaten to limit intellectual property protection or constrain market size for new anti-infectives would of necessity cause companies to invest their research effort in other, more profitable, therapeutic areas. This would inevitably jeopardise therapeutic progress leading, ultimately, to a worsening of the problem of infection control.

2. VETERINARY USE OF ANTIBIOTICS

The widespread use of antibiotics in animal husbandry and veterinary care has attracted a long and extensive debate on its implications to human healthcare. The situation is well summarised in the World Health Report (WHO, 1996) which states

“More than half of the total production of antimicrobials worldwide is currently used in farm animals, with a large proportion of antibiotics being administered in sub-therapeutic doses, not to treat disease but to promote growth. This practice is contributing to the development of multiresistant strains of bacteria such as salmonellae and *E. coli* in animal production that gets transferred to humans through meat or other food of animal origin or through direct contact. The prevalence and implications of antimicrobial resistance connected with food from animals are however inadequately understood” WORLD HEALTH REPORT 1996, WHO.

Concern over transfer of antibiotic resistance extends far wider than the Gram-negative enteric bacteria mentioned above. For example, earlier this year, the use of the glycopeptide avoparcin in animal feedstuffs was banned by the EU and Switzerland because of concern of transfer from veterinary strains of enterococci. Although present evidence linking glycopeptide-resistance in animal isolates with human pathogens is not compelling, the directive was given as a precautionary and protective measure in the current climate of doubt.

We support this stance and believe that there is now sufficient experience in antibiotic use (both human and veterinary) to appreciate that the use of antibiotics *per se* leads to the selection of antibiotic resistant bacteria. In general, the greater the use of a particular antibiotic, the greater the potential for resistance. Close monitoring of bacterial susceptibility to all antibiotics is necessary to minimise any negative impact on human healthcare.

For this reason, we believe that veterinary antibiotic use should be restricted to:

1. treatment of a specific, sick animal (short course therapy)
2. short term treatment of an epizootic in sick animals (short course therapy of the sick and simultaneous short course prophylaxis of the remainder of the herd/flock). We understand both from a practical viewpoint (the difficulty of separating from a large herd/flock the infected animals for treatment) and from a social viewpoint (putting a farmer's livelihood at risk) the need for prophylaxis in this instance.

Practices which are likely to generate an unnecessary risk of selection for antibiotic resistance and subsequent transfer to man should not be permitted. These include:

3. long term treatment/prophylaxis of an outbreak of sick animals. This practice can involve therapeutic doses of antibiotics being administered for weeks/months, for example over the winter months, to prevent recurrence of outbreaks.
4. Sub-therapeutic doses of antibiotics for growth promotion.

It has been argued that [4] above is acceptable provided the antibiotic has no counterpart in human medicine. We do not subscribe to this view for two reasons. First, given the urgent need for new antibiotic classes for human use and the renewed interest in “neglected antibiotics” as potential sources of such drugs (see section 1), no family of antibiotics should continue to be regarded as being restricted to veterinary use. The development of Synercid for serious hospital infections is a prime example here. Further examples are likely in the coming years as combinatorial chemistry approaches are applied to other antibiotic series. Secondly, decreases in susceptibility to a wide range of antibiotics can come about via mutations affecting molecular pumps (efflux mechanisms) which act to prevent antibiotics accessing their molecular targets. These pumps can act on highly diverse molecular classes and the risk of emergence cross resistance with unrelated antibiotics cannot be accurately predicted.

3. ISSUES RELATING TO THE PRESCRIBING OF ANTIBIOTICS

There is increasing concern from patients and from the public health regarding the development of bacterial resistance both in hospitals and in the community. Particularly worrying is resistance developing in organisms to multiple classes of antibiotics. Public health concerns are mirrored by the concerns of governments, regulators and the microbiological and clinical communities.

Key clinical and scientific opinion leaders often talk about the “inappropriate” use of antibiotics driving bacterial resistance. In countries in which antibiotics are freely available without prescription, this is likely to be true, if only from a Darwinian perspective whereby selective pressure for resistance will increase as

antibiotic exposure increases. However in countries with controlled prescribing such as the UK, the prescriber, who is usually a general practitioner, is faced with a number of issues which render the very concept of “appropriate” and “inappropriate” prescribing simplistic, and certainly without much factual basis. These issues include:

- Uncertainty as to whether a particular patient is suffering from a bacterial infection. More often than not, when the patient walks through the door, the doctor does not know this.
- The choice of antibiotic is essentially empiric or based on previous experience. Data on local resistance patterns and their relationship to defined clinical outcomes are not usually available.
- Only a proportion of those treated will benefit from antibiotics. Some infections are self limiting (or are viral) and it is not possible to define those patients individually. The lack of such a feedback loop prevents the identification and assimilation of “best practices” to improve prescribing habits.

The problem is that clear, clinical outcomes related to antibiotic use are relatively undefined. Clinical trials required for registration and post registration do not differentiate adequately between different antibiotic products let alone determine value for individual patients. The reasons for this are many but include:

- the fact that antibiotic studies are not generally placebo-controlled (in most cases it is considered unethical); and
- patients are recruited without full knowledge of the bacteriology. Furthermore, it may not be possible to monitor this throughout the study. (eg for patients with earache, it is not usually possible to determine the causative organism before, during or after treatment because isolation of pathogens from the middle ear is not possible without the highly invasive procedure of piercing the eardrum).

Since clinical trials do not determine the most appropriate treatment for a given indication or place a value on specific treatments for individual patients, the means by which “appropriate” antibiotic usage can be assessed is problematic. Ultimately this information, together with data on the changing local antimicrobial susceptibility patterns, needs to be provided at the point of care to permit prescribers to select prescription medicines wisely.

The form of “evidence-based” selection is seen to be far more preferable than strict, often arbitrary, controls to limit the selection of drugs available to prescribers. The latter approach is based on the simplistic notion that “antibiotic use is linked to antibiotic resistance”. The corollary (that by restricting antibiotic use, one would better control resistance) is flawed because it takes little account of the value of a given course of antibiotic nor its likely impact, if any, on bacterial resistance. Evidence-based prescribing is of universal benefit; not only to the patients, payers and prescribers, by enabling the selection of the most appropriate, cost-effective therapy, but also to the pharmaceutical industry by providing an appropriate environment in which to operate competitively.

For many infections (especially those in the community) adequate definition is lacking for both (1) the economic and clinical value of particular antibiotics and (2) the impact of bacterial resistance/decreased susceptibility to those antibiotics.

What is needed is a significant improvement in the external validity of clinical trials. In particular:

- better definitions of who benefits and by how much;
- better data on long term effects of antibiotics on the microbial population through surveillance both in infected patients and in the normal hosts; and
- better data on resistance development and most particularly on the impact of resistance on outcomes as well as the impact of prescribing on outcomes.

SmithKline Beecham is committed to the transformation of antibiotic use through information-based strategies and evidence-based outcomes analysis. We are actively looking at all sources of information, whether it be the information linking (1) the development of resistance to the activity of the antibiotic on the specific organism, (2) use of our product to the development of resistance to that product and to other antibiotics. Through database mining, we are looking to see if we can dissect out (1) the influence of antibiotic use on resistance, (2) the influence of antibiotic use on outcomes and (3) the influence of resistance on outcomes. In addition, SmithKline Beecham recognises that new alliances between governments, public bodies such as WHO, CDC, PHLS, prescribers and the healthcare purchasers need to be formed.

4. ANTIBIOTIC RESISTANCE SURVEILLANCE

How far is the Industry co-operating with health services, the PHLS, the WHO and other bodies in surveillance and investigation of resistance to antibiotics?

The value of monitoring and investigating antibiotic resistance has been recognised by SmithKline Beecham and other pharmaceutical companies involved in antibiotic discovery and development for some time. Only through a continuing assessment of both the nature and extent of antibiotic resistance can the medical need, and the commercial value of a new product or class of products be evaluated. Investigation of

the mechanisms of resistance is also vital to allow targeted preventative strategies, including the appropriate use of existing antibiotics and the development of new antibiotics to overcome resistance mechanisms.

Industry has funded such studies, working in conjunction with external clinical microbiology centres and research institutions, many of which are associated with national bodies, such as the PHLS in the UK. Data from the majority of these are published in peer reviewed scientific journals and the findings are often incorporated into the framework of national treatment guidelines. Although undoubtedly valuable, they tend to be sporadic in nature and frequently involve isolates picked from referral centres (which may be non-representative of the population as a whole). Furthermore, inter-laboratory variability in methodology and differing criteria for the assessment of resistance inevitably reduce their impact such that they can only give a partial indication of changing patterns of resistance.

In recent years, SmithKline Beecham has been at the forefront of a movement to address the lack of more global, longer term studies to monitor changes in resistance patterns over time and to assess the reasons for local and geographical differences. One such study, the Alexander Project, was initiated in 1992 and has produced high quality susceptibility data for the major respiratory pathogens from Europe and the USA. Susceptibility data were generated by an independent single UK-based laboratory on a range of 16 standard antibiotics representing the major antibiotic members and classes for use in the community. The methods and assessment criteria were established by an international panel of experts at the initiation of the project. Data generated from 1992 to 1995 have been presented at conferences and published in peer review journals. In 1996 the scope of the project was expanded to include further countries from Europe and also Asia and Africa. These data are currently being analysed for publication. Future expansion of the Project is underway with the guidance of a steering committee of infectious disease experts, many of whom sit on international or national bodies responsible for antibiotic policy.

New global surveillance studies, wholly or jointly funded by Industry are now emerging along the lines of the Alexander Project (it is imperative, however, that the quality of data through consistent methodology and assessment criteria for all the isolates be defined proactively). Such studies include the Sentry study funded by Bristol Myers Squibb which will collect isolates from 200 centres world-wide. Results will be made available to participating hospitals to enable changes in therapy if appropriate.

SmithKline Beecham and other industrial partners have also been in close contact with international and national bodies, such as the WHO, with respect to the design and funding of other surveillance programmes. SmithKline Beecham contributed to funding for the worldwide establishment of the WHONET network for collection of susceptibility data from a range of national laboratories. One key issue with WHONET and other projects reliant on locally generated data was the variability in type and quality of data which was to be collated onto the database. SmithKline Beecham also brought together a group of experts involved in surveillance programmes to explore the concept of "Centre of Excellence Laboratories" (COELs) to aid the process of establishing more centres, particularly in developing countries where data of a suitable, comparable quality could be generated. It was believed that this process would also lead to the COELs influencing further local laboratories to adopt good quality test procedures, thus adding to the pool of usable data and enabling fact-based local prescribing.

The WHO, which was represented on the SmithKline Beecham-funded COEL Advisory Board has expanded the WHONET and COEL concepts further into a proposed network of laboratories which will test isolate susceptibility to an agreed quality standard. SmithKline Beecham contributed to the funding of the training manual and leaflet on the WHO Network on Antimicrobial Resistance Monitoring and continue to maintain discussions with WHO on the conduct of surveillance and the use of the data. SmithKline Beecham continues to liaise with WHO on how WHO and Alexander Project data may be shared or combined with other data. A wide range of representatives of the diagnostic and pharmaceutical industry (SmithKline Beecham, Rhone-Poulenc Rorer, Hoffmann-La Roche, Ciba-Geigy, Bayer, Solvay Duphar, Zeneca, Pfizer, Schering-Plough, Lilly, Wyeth-Ayerst) along with the International Federation of Pharmaceutical Manufacturers Association (IFPMA) have been involved in discussions on the expansion of the WHO surveillance and the potential role for industry collaboration. The WHO have recently redefined their programme as a result of discussions with industry as the WHO programme on Antimicrobial Resistance Monitoring (ARM-EMC) and a "contact group" of industry representatives is being established through IFPMA.

Industry is also involved in the design and funding of many national and regional surveillance programmes. For example in the UK, SmithKline Beecham and Zeneca are represented along with PHLS members on the British Society for Antimicrobial Chemotherapy Working Party on Antibiotic Resistance and currently involved in discussions on a protocol for UK-based surveillance studies. Nationally recognised studies are conducted in many countries or regions (France, Italy, Spain and Asia for example) with industry funding and resource. Overall, SmithKline Beecham is funding microbial susceptibility surveys in over 50 countries.

Industry is continuing to explore ways of making surveillance data available to clinical microbiologists and prescribers in a timely and appropriate manner to aid local prescribing decisions through local data-bases of surveillance patterns and interpretations. This is expected to improve local prescribing patterns.

In addition to generating susceptibility data, industry is also working to aid its interpretation. Criteria such as individual drug pharmacodynamics are incorporated in the analysis so that decisions on the most appropriate choice of antibiotic can be made in the knowledge of the most likely pathogens for a particular

infection, their susceptibility in the locale, and the optimum choice of antibiotic to result in bacterial eradication. The intention of such measures is to reduce the potential for recurrence, relapse, transmission and increase in resistance.

Modelling and predicting resistance trends are also being undertaken. For example, SmithKline Beecham and other industry members are actively involved in collaboration with groups at Oxford University, the Wellcome Trust, Emory University, and the CIBA Foundation to understand and model the causes and effects of antibiotic resistance. Good quality longitudinal trend surveillance data, along with antibiotic usage and outcome data are essential for these studies and the industry has a major role in supporting the generation and use of these data.

SmithKline Beecham and other companies with extensive R&D investments in antibiotics are taking the issue of antibiotic resistance surveillance very seriously. It is recognised that the problem of antibiotic resistance is complex and that appropriate solutions are likely to arise only through the generation, interpretation and modelling of extensive surveillance data. These data, in combination with information on antibiotic use patterns and pharmacodynamic information, can then form the basis of active dialogue between all interested parties to generate optimal frameworks for prescribing guidelines.

Given the commercial environment in which the pharmaceutical industry operates, it is in a unique position to fund the generation of much of the underpinning data, which it does willingly and with the goal of an increasingly evidence-based approach to antibiotic usage in mind. This is seen as a far more beneficial approach than say, one based on undue regulation and inflexibility. Indeed, the very ability of industry to play this important role is dependent upon the maintenance of a favourable commercial climate. Undue constraints on antibiotic use run the risk of stifling not only the industry's R&D investment in new anti-infective agents but also the generation of surveillance data and associated research tools designed to ensure optimal usage of the current antibiotic arsenal.

5. SWITCHING PRESCRIPTION ANTIBIOTICS TO OVER-THE-COUNTER PRODUCTS

Is there a link between antibiotic OTC use and resistance?

The use of non-prescription, "Over-The-Counter" (OTC) antibiotics in the developing world and some southern European countries such as Spain has, in the opinion of many experts, caused significant increases in bacterial resistance in those countries. The reality is that in common with almost all aspects of bacterial resistance, there is a lack of data with which to make scientifically informed judgement. What is required in a specific country is much greater information on changes in bacterial antibiotic resistance rates over time together with details of prescription and OTC antibiotic usage. The antibiotic resistance data will require extensive, longitudinal antibiotic resistance surveillance programmes. The antibiotic usage data must include, for example, the number of daily doses per 1,000 of the antibiotic population as well as similar data for use as prescribed by the doctors and dispensed by the pharmacists.

It is only by performing such scientifically robust studies, both retrospectively as well as prospectively, that appropriate policies to control bacterial resistance will be identified and enacted.

PART B ANTIVIRALS AND ANTIPARASITICS

6. RESISTANCE IN VIRAL INFECTIONS

The pattern of drug resistance in viruses has been very different to that seen with antibacterials. Anti-viral therapies to date have not been broad spectrum and the oldest effective anti-viral therapies have only been in place for the last two decades compared to more than five decades for anti-bacterials. Anti-viral resistance has been very dependent on both virus type and patient group.

6.1 *Herpes viruses*

The systemic treatment of herpes infections with nucleoside analogues (acyclovir and subsequently famciclovir and valaciclovir), represented the first truly effective anti-viral therapies. In immunocompetent subjects, the prevalence of resistance to therapy was 0.3-3 per cent (depending on methodology used to test for resistance) prior to the licensing of any nucleoside analogue. Despite nearly two decades of use, it has remained unchanged. By contrast, resistance is more frequent in the immunocompromised (HIV, cancer, bone marrow transplant patients) with rates as high as 2-11 per cent in HIV patients receiving long term herpes prophylaxis. It is unclear if the incidence of resistance is increasing in this population. In part, the lack of resistance is due to the essentiality of the anti-viral target in determining virus viability and transmissibility. These resistant viruses appear to be less effective at replicating than wild type virus and have limited ability to transmit to other individuals. Consequently spread of resistant virus is limited.

6.2 *Human Immunodeficiency Virus (HIV)*

The pattern of resistance in HIV is very different. HIV is a much less complex organism than the herpes viruses and consequently has a much greater latitude for biological diversity, without compromising its viability and host interactions. Its replication in humans is very imprecise and carries a high natural mutation rate, leading to the rapid generation of divergent virus strains. In the presence of the selective pressure of anti-viral agents, this rapidly leads to the development of drug resistance and the precise mutational event conferring drug resistance can be precisely characterised. Monotherapy of HIV with Zidovudine leads to the generation of resistant virus within six months of therapy. To tackle this challenge the Pharmaceutical industry has developed a number of novel HIV therapies that either target different enzymes within the virus (protease inhibitors) or act at a different site within existing anti-viral targets (reverse transcriptase inhibitors). Resistance develops rapidly when these new agents are used as monotherapy. Combination therapy with up to three drugs, in a fashion analogous to the treatment of TB, has been applied to HIV. These treatments have been very successful to date, but the duration of therapy has been too short to draw any definitive conclusions on the propensity of the virus to become resistant to all three agents.

Transmission of resistant HIV strains is likely to be limited in the face of effective safe sex campaigns, although the increasing practice of some high risk uninfected individuals to take illicit triple therapy as a “morning after” post-exposure prophylaxis will most likely select for transmission of resistant virus to those individuals.

6.3 *Hepatitis B virus*

The other virus that has become a realisable goal of antiviral therapy is Hepatitis B virus. New anti-viral therapies are in phase III clinical trials. Evidence to date suggests that drug resistance may follow the HIV model, with reports of resistance to monotherapy occurring in up to 20 per cent of patients treated in the first year of therapy with lamivudine. Combination therapy may be required to control this virus. Effective protection of uninfected individuals by hepatitis B vaccination should limit any potential for spread of resistant hepatitis B virus.

6.4 *Anti-viral prospects*

The understanding of the biology of viruses of medical importance has been greatly facilitated by the generally small size of viral genomes with the ability to sequence the genomes and assign function to viral proteins. This has allowed the rapid selection and exploitation of rationale targets for drug discovery and development.

A combination of available technology, unmet medical need, opportunity for significant commercial return and likely rapid development times and accelerated approval have all made the HIV and to a lesser extent the Hepatitis B areas of significant interest to the Pharmaceutical industry. The challenge of anti-viral drug resistance is being met by the Pharmaceutical industry providing a rich heritage of newly developed anti-viral drugs and a willingness by patients, physicians and regulatory bodies to move to a “TB treatment paradigm” of combination therapy.

Viral drug resistance is very different to bacterial drug resistance. Most of the drug resistance has not been transmitted to any significant degree between subjects, although this may reflect the relative infancy of anti-viral therapy. Technical breakthroughs in anti-viral drug discovery and development appear to be keeping pace with viral drug resistance at the current time.

7. RESISTANCE IN PARASITIC INFECTIONS

7.1 *Background*

Parasitic diseases are essentially most prevalent in developing countries and the understanding of parasite biology, drug resistance mechanisms, and resistance epidemiology is far less well developed than for bacterial and other infections more commonly encountered in the developed world. Difficulties of studying protozoan and metazoan organisms in culture and of quantifying drug resistance, together with poor laboratory facilities in many countries, hamper the evaluation of potential drug-resistant strains. The issue of parasitic drug resistance is further complicated by irrational drug use, poor quality generic medicines, poor patient compliance, poor understanding of drug use by physicians, paucity of new medicines and lack of longitudinal data on which to base evidence of emerging resistance.

It is therefore hardly surprising that parasitic resistance to drugs has arisen in the first place, and that knowledge of the extent and nature of that resistance is so poor. In many parasitic diseases (eg Leishmaniasis, Trypanosomiasis, Schistosomiasis, Onchocerciasis, Filariasis and helminth infections), it is often difficult to differentiate increasing drug resistance from treatment failures due to poor compliance and old, only partially effective and toxic medicines. Malaria is an exception.

7.2 Malaria

7.2.1 *Plasmodium falciparum*

Drug resistance in malaria, especially in *Plasmodium falciparum* (malignant tertian malaria) is well documented. Since the late 1970's it has been possible to grow *P. falciparum* in culture and to study drug sensitivities *in vitro* rather than rely solely on clinical evidence from field isolates. Even so, resistance determined *in vitro* does not correlate well with drug failure *in vivo*, mainly due to host features such as drug kinetics and metabolism which confound the picture. Since World War Two, there has been a progressive loss in the number of effective drugs for the treatment and prophylaxis of malaria, due to the development of drug resistant *P. falciparum*. The molecular mechanisms behind this are multifactorial and differ with each drug. In general, it has not been possible to overcome many of these mechanisms, although drugs appear to remain partially effective. Differences in the epidemiology of resistance are also evident. Chloroquine resistance appeared initially virtually simultaneously in SE Asia and S America, and progressed outwards from these centres. This shows that, despite widespread and equivalent use in other parts of the world, this form of resistance arose from a limited number of resistant strains, arising independently. In contrast, antifolate resistance is known to be caused by simple genetic mutation and seems to be directly related to the level of drug use.

The major problem with drug resistant *P. falciparum* is that the number of alternative drugs is severely limited, and of those that are available, many are closely related giving rise to the problem of cross-resistance. Drug resistance to two of the most recent introductions (mefloquine, halofantrine) is already described from many sites around the world, and in some areas (eg SE Asia), mefloquine has become virtually useless when used alone. In East Africa, highly mefloquine-resistant strains were described before the drug had ever been used there.

The evidence to date suggests that for *P. falciparum*, the effective lifespan of a widely used drug is unlikely to exceed 5-10 years, especially in Africa and SE Asia. On this basis, a minimum of three new compounds would be needed per decade just to maintain the status quo. This situation was reached only once, in the decade immediately after World War Two and to confound matters, the new compounds that are required now need to be unrelated to those in which drug resistance has been identified. However, if further antimalarials acting on different molecular targets can be developed, combination therapy regimens to prolong significantly the life of these products may become a real possibility.

In the short term, this requires careful evaluation of the extensive research work that has been done around the world. However, traditional methods are extremely labour intensive. Despite this, the US Army Malaria Research Programme screened in excess of 300,000 compounds in the past 30 years. Even this major effort has led to the development of only two compounds to date (mefloquine and halofantrine). In the longer term, it is likely that parasitic genomics will eventually provide new molecular targets for antiparasitic drugs but this is unlikely to impact available therapies for > 10 years.

Since the immediate picture appears to be bleak, it is encouraging that a number of compounds are currently under development. These include atovaquone/proguanil (Malarone: Glaxo Wellcome) which has been approved for treatment, and is being looked at for prophylaxis, co-artemether (Novartis), pyronaridine (WHO), WR 238605 (SmithKline Beecham) and Chlorproguanil/dapsone (WHO/SmithKline Beecham).

Potential issues surrounding several of these compounds include:

- While atovaquone/proguanil is very effective at present, it seems, based on the development programme that proguanil is essential to protect atovaquone. Currently proguanil resistance is not a problem, but it is unknown what would happen if this became widespread.
- Co-artemether is in late stage development, and by using two compounds together may protect and prevent future resistance. However the results from clinical trials show relatively poor efficacy in comparison to quinine and halofantrine.
- Pyronaridine has been under investigation for many years, and as a simple molecule has much to recommend it. However animal studies suggest that resistance development under drug pressure is probably faster than with any other compound yet investigated, and there is also evidence of cross resistance with chloroquine.
- WR 238605 is a promising compound for treatment and prophylaxis based on the animal and early clinical studies. It is however early in development.
- Chlorproguanil/dapsone is a short half-life antifolate combination which is being developed to fill the gap produced by drug resistance to sulphadoxine/pyrimethamine (Fansidar) in Africa. It is recognised that this is a stop gap measure, and that resistance may rise quite rapidly to this combination.

These candidates are likely to be much more expensive compared to the products that they are replacing, mainly because the cheaper options have already been exhausted. One of the future goals must be to find affordable options as well as effective ones since the majority of users of antimalarials live in circumstances where they cannot afford more than minimal cost. At present, those drugs which are available are often used at sub-optimal doses to reduce expense. An essential issue related to the slowing of the development of

resistance is the proper use of the drugs we have. This must include the rational use of single agents and of combinations (including new combinations).

In the case of *falciparum* malaria, there is a recently highlighted approach to prevent drug resistance. Evidence from Thailand suggests that since the deployment of artemisinin in the endemic Western Border region, there has been a dramatic reduction in the rate of transmission of malaria, and also in the development of drug resistance. This is not connected with vector control, but with the transmission-blocking activity of the compound. While this compound appears to be effective, the new compound atovaquone/proguanil and also WR 238605 are more potent. Strategies which utilise transmission-blocking drugs have the potential to limit malaria in the community, and in so doing, reduce the risk for the spread of resistance. This area of drug development is in its infancy, and requires considerable commitment to achieve scientifically valid data with which to build drug control strategies.

7.2.2 *Plasmodium vivax*

Drug resistance in acute benign tertian malaria is more recent in origin, the first cases being described from Indonesia about 10 years ago. The spread of drug resistance is slower, because the transmission and replication rates of this parasite are much lower than with *P. falciparum*. Currently resistance of *P. vivax* has only been described to chloroquine, and most other drugs are still very effective. For the time being, it is likely that drug developments for *falciparum* malaria will outstrip the development of resistance in *P. vivax*. One feature of *P. vivax* is that it produces dormant forms of the parasite in the liver which can cause recurrent attacks over many years. Only one drug, primaquine, is available to prevent these attacks, and there is clinical evidence of increasing drug failure in some parts of the world. A more potent analogue of primaquine, WR 238605 is in development, but it is unclear whether this will be potent enough to overcome drug resistance to primaquine.

7.2.3 Other Human Malarias

Drug resistance in *P. malariae* and *P. ovale* have never been described, and it is likely that the current drugs available will remain effective for these rarer infections.

7.3 Anti-parasitic Prospects

Research into the treatment of parasitic diseases and other so called "tropical diseases" have suffered from a relative lack of investment over the last 25-30 years. Resistance to the available anti-malarial drugs is recognised and the subject of significant R&D effort by the industry.

Treatment of other infections predominating in the developing world is much more problematic when reliance still has to be placed on old and at best partially effective remedies. Although the evidence for true drug resistance is at present poor for most parasitic diseases, the evidence from veterinary medicine indicates that this is a real possibility. If one is to learn from the experience of malaria, it is essential that strategies are put in place to provide new medications ahead of the need, rather than hoping that the problem will never arise. By the time that it is recognised that resistance is established, drug development will be lagging far behind the need, and the impact of resistance will be all the greater in some of the most prevalent and debilitating diseases on the planet. The real barrier to further commercial investment in this area is that the major investment in new technologies required cannot be readily justified on commercial grounds.

If the pharmaceutical industry is going to play an increasing role in developing treatments for these diseases, it is imperative that interested parties (governments, the pharmaceutical industry, healthcare workers, WHO, Non Governmental funding agencies) tackle this issue. The "global village" is becoming a reality and the danger that some of these diseases become far more widespread is of significance to all countries, including the UK.

In this regard, the strategy followed by the US in drug development for malaria is a good example of enlightened self-interest, with the US Army (for good military strategic reasons) funding the early development of compounds and then working with industry to ensure that they reach the market. SB has been a beneficiary of a number of these (halofantrine, WR 238605, and WR 6026 got leishmaniasis). In the latter two cases there is an agreement to refund the US Government some of the initial costs (but no profit) through a limited royalty on sales. It is interesting to note that the Department for International Development at SmithKline Beecham is looking at some of the above issues in relation to the UK aid programme, and their recognition that parasitic diseases and potential or real drug resistance are a threat to development, and to their programmes.

PART C VACCINES

8. PROSPECTS FOR NEW VACCINES

8.1 *Classic vaccines*

Vaccines have been used in the prevention of infectious diseases for 200 years. They were traditionally produced by identifying the pathogenic agent, inactivating it by heat or formaldehyde or attenuating it by prolonged culture. These almost entirely empirical procedures yielded vaccines for smallpox, polio, tuberculosis, yellow fever, whooping cough, measles, mumps and rubella. Also vaccines for diphtheria and tetanus were produced by inactivating (toxoiding) the toxin secreted by *Corynebacterium diphtheriae* and *Clostridium tetani*, respectively.

Today, immunisation programmes exist in every country in the world and immunisation is one of the safest, and possibly the most cost effective, of all medical interventions. Smallpox has now been eradicated and polio, already eradicated from the Americas, should follow soon, thanks to the current worldwide immunisation campaign.

8.2 *Future prospects*

Vaccine design will be based increasingly on an improved understanding of the immune responses involved in pathogen clearance versus pathogenesis, and the ability to induce selectively these various effector immune responses.

Recombinant DNA technology has made it possible to work with genes of disease-causing organisms enabling the identification of potential vaccine targets. Furthermore, as with the development of new antibiotics, genome-based approaches provide the opportunity to identify hitherto unknown potential vaccine candidates. Theoretically, this could result in (1) vaccination with nucleic acids to induce antigen production by the vaccinated host itself, (2) vaccines based on pathogen modifications which give rise to decreased pathogenicity and/or enhanced immunogenicity, (3) the development of recombinant live viral or bacterial vectors expressing protective antigens and (4) purified antigens produced by genetically engineered cells.

Adjuvants and delivery technologies that improve vaccine efficacy by selectively enhancing, modulating and/or targeting an effective immune response to elicit the desired balance between cellular and humoral immunity, are also under development.

Furthermore, although vaccines have traditionally been used in disease prevention, attempts are being made to discover those which are effective in the treatment of established disease (therapeutic vaccines). These would act by enhancing the patients' own ability to fight and contain an infection. The ability to stimulate selectively appropriate effector immune mechanisms associated with particular infections will be critical to success.

All this has led to an explosion of activity in vaccine research and development. According to the 1996 "Biotechnology Medicines in Development" survey of the Pharmaceutical Research and Manufacturers of America (PhRMA; Washington DC, USA) the number of biotechnology-derived vaccines in development has increased by more than 40 per cent since the 1995 survey. 18 (29 per cent) of the product candidates listed are prophylactic vaccines for the prevention of diseases such as Lyme disease, whooping cough, genital herpes and diseases mediated by respiratory syncytial virus, whereas 44 (71 per cent) are therapeutic vaccines for the treatment of various infectious and non infectious diseases.

8.3 *Target organisms for vaccination*

The Ad Hoc Committee on Health Research Relating to Future Intervention Options identified in their report "Investing in Health Research and Development" (World Health Organisation, Geneva, 1996, Document TDR/Gen/96.1) four communicable diseases as sources of major threats to all populations: tuberculosis, pneumococcus, malaria and the cluster of sexually transmitted diseases including HIV/AIDS. Vaccine prospects for these and for the prevention of hospital infections are briefly summarised.

8.3.1 *Tuberculosis*

The currently used attenuated BCG vaccine was first tested and shown efficacious in 1928. Since then, efficacy has been found to be highly variable (from about 80 to 0 per cent) in several controlled trials. Although recent advances in basic mycobacterium research, especially in immunology and genetics, make development of new vaccines a realistic possibility, a major problem remains. In humans, the nature of protective immunity is not well understood and correlates of protection or surrogate markers of effective immunity are not available. Moving promising vaccine candidates into clinical evaluation continues to be a considerable challenge.

8.3.2 *Pneumococcal disease*

Available multivalent pneumococcal vaccines do not induce protective immunity in infants below two years of age. However, vaccines suitable for infants are now in advanced stages of development. These are based on antigens derived from the bacterium's outer layers (capsule) that are conjugated to protein carriers. Different isolates have different capsule components and these vaccines are multi-component so as to match as closely as possible the mix of subtypes that cause most invasive infections. Since not all subtypes can be accommodated in a single vaccine, there is a concern that some of the less frequent ones (not covered in the new vaccines) could become more prevalent over time.

However, the pneumococcal vaccine is similar to the new generation of *Haemophilus influenzae* type b vaccines, licensed at the end of the 80s. Since their introduction, *Haemophilus influenzae* colonisation and disease has all but disappeared in the US and many northern European countries, including the UK. Similarly, the new generation pneumococcal vaccines may both prevent pneumococcal disease and reduce (vaccine-specific) pneumococcal colonisation in vaccine recipients. The latter property might indirectly prevent disease by reducing spread of infection.

Several Phase III efficacy studies are ongoing and it is expected that the new generation of vaccines will become available within the next five years.

8.3.3 *Malaria*

Complexities in the life cycle of the parasite and the human immune response to it, have made vaccine development difficult and currently no vaccines are in an advanced stage of development. Recently, a SmithKline Beecham candidate vaccine was shown to have protected a small group of immunised volunteers from a controlled experimental challenge with the parasite. This candidate vaccine will be subjected to a limited field trial to investigate whether efficacy is confirmed under field conditions and whether further development is warranted. Optimistically, this vaccine could be available for widespread use in 10 years time.

8.3.4 *HIV/AIDS*

Recent advances with combinations of antivirals are encouraging. However, the emergence of resistance to single antivirals has been rapid. It remains to be determined if and with what rapidity viral populations resistant to antiviral combinations will emerge.

The need for a safe, efficacious vaccine is paramount. Multiple approaches to develop prophylactic as well as therapeutic vaccines are being tested at preclinical and clinical level. None of these approaches to develop an HIV vaccine seems likely to succeed in the immediate future, given the probable need for a broad based immune response which is directed against multiple antigens and encompasses various effector immune mechanisms, to prevent or control the infection effectively. Despite major advances therefore, a greater understanding of HIV and its interaction with the human immune system is needed before effective vaccines are likely to be developed.

8.3.5 *Nosocomial (hospital) infections*

A major concern in the developed world is the emergence of antibiotic resistant bacteria in hospitals and care facilities. The incidence of acquiring an antibiotic-resistant infection upon hospital admission increased progressively during the last decade. Most frequent are infections with *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci and *Escherichia coli*.

Today, approaches to *Staphylococcus aureus* vaccines are only in early stages of research, and there are no immediate prospects for vaccine development. Even if an effective vaccine to prevent *Staphylococcus aureus* infections becomes available, the larger problem of nosocomial infections would not be addressed effectively. Nosocomial infections are due to a variety of at least 30 different pathogens. Their relative proportion shifts in response to medical practices in general and to the antibiotics in use. Prevention of *Staphylococcus aureus* infections would most likely lead to the emergence of another pathogen as a major threat.

However, since the incidence of nosocomial infections is a direct function not only of pathogen dose and virulence but also of host resistance, methods to enhance host immunity in general, may impact the overall attack rate. Indeed additional approaches to the prevention and treatment of infection by immune modulation are also being investigated by SmithKline Beecham and other companies. These would involve the administration of agents which directly or indirectly activate neutrophils and monocytes or which possess appropriate anti-inflammatory activity (eg in certain viral diseases where the observed pathology is mediated by a range of cytokines implicated in direct tissue damage or in the recruitment of additional inflammatory cells). These approaches are still highly speculative but may complement vaccines and conventional antibiotic therapy in the control and treatment of infection.

As hospital admission is a planned event only in some instances, the application of prophylactic vaccination and indeed other means of immune modulation alluded to above, will always have its limitations in this setting.

8.4 *Vaccines and the control of infectious diseases*

Vaccination is unlikely to resolve all problems associated with infectious diseases since it is based on equipping the host defence system for the struggle with pathogenic invaders. This requires a certain build-up of immune recognition mechanisms. In general, already declared acute life threatening infections are not amenable to control by vaccination. However, vaccination can be a very efficacious means to prevent infections, and may become an effective way to treat and possibly cure patients from chronic or recurrent diseases in the future.

However, the predicted breakthroughs in new vaccine development will not fulfil their promise if further public and political awareness of the health benefits and the cost-effectiveness of vaccination are not forthcoming. Present and future vaccines will need to be used more widely throughout the world to realise their full potential.

PART D RECOMMENDATIONS TO GOVERNMENT

New strategies for the treatment and prevention of infectious disease are an important and urgent priority driven by the alarming escalation of microbial resistance to existing antibiotics and the dearth of new antibiotic introductions anticipated over the next five to seven years. These are, however, tangible opportunities for the discovery and development of new therapeutic agents and vaccines. These opportunities arise first from a re-examination of neglected or under-exploited antibiotics and secondly from the promise afforded principally from genomic and other technological advances. To realise these opportunities requires government encouragement of pharmaceutical R&D and strong support for intellectual property protection.

The pharmaceutical industry, with its enormous drug development costs and demand by shareholders for return on investment, will only invest in this therapeutic area if there is a clear commercial opportunity as well as unmet medical need. Restriction of industry's return on investment will adversely affect this and prompt a move away from pharmaceutical R&D in anti-infectives into other, less restricted therapeutic areas. The support and encouragement by governments to the Pharmaceutical industry to meet the challenge of HIV has led to the rapid emergence of a range of valuable and effective agents to combat this disease, also assisted by a dramatic revision of regulatory standards and enhanced regulatory flexibility. The precedent set by the government and industry response to HIV is a model of the partnership required to bring forward new agents to combat the rising threat of drug resistant organisms.

The protagonists of the view that antibiotic usage should be severely restricted (because we have precious few antibiotics with which to tackle bacterial infection in the face of ever increasing resistance) will deny industry the incentive to discover and develop new agents. Their alarming prophesies are in this sense self fulfilling, since industry will not produce the next generation of agents if they cannot be adequately compensated for the cost of high risk R&D investment.

New surveillance procedures and tools to model and detect early trends in antibiotic resistance changes are likely to improve the use of current agents. The provision of local, regional/national and global microbial susceptibility data, linked to pharmacodynamic predictors of clinical outcome, will provide an increasingly sophisticated database for effective, rational prescribing. Given the speed with which resistance to anti-infective agents can (and do) arise locally, it is unlikely that curbs on antibiotic prescribing will provide the optimum means of controlling antibiotic use.

However, for these opportunities to be realised, it is evident that the UK/European commercial, regulatory and scientific climate must be geared to:

- support and encourage industry to invest in the discovery and development of new classes of antibiotics and other novel approaches for combating microbial diseases;
- streamline requirements for clinical development and registrations. For example, this could be achieved by:
 - (1) shortened timelines from regulatory filing to approval/registration. The normal time is around a year but two HIV protease inhibitors took substantially less time, Norvir (182 days) and Indinovir (217 days).
 - (2) a review of the potential for simplified, faster development programmes that could be adopted in which greater use is made of pharmacokinetic surrogate markers (simple indirect markers of likely drug effect), linked to tissue distribution and penetration data and safety data. Clinical studies with fewer patients (trovafloxacin, a recent antibiotic in registration, involved a vast population cohort of 13,000 patients in trials) could be used to speed development, particularly if coupled with more extensive Phase IV studies to address neglected issues, for example those relating to improved clinical outcomes. A precedent for faster, simpler development is found in the registration by SmithKline Beecham of a bd (twice a day) formulation of Augmentin. This was based on an abbreviated development package, encompassing a phase III safety study and an acceptable pharmacokinetic rationale. This showed that the twice a day dosing was equivalent to the previously registered three times a day dosing.
- support development of point of care diagnostics so that antibiotic prescriptions are given to the patients who are diagnosed as having a definitive bacterial infection and will benefit from the specific

antibiotic selected. This could be supported through, for example EU Foresight investments in diagnostic technology;

- encourage rational prescribing of antibiotics by encouraging wider antimicrobial surveillance measures and the widespread availability of robust diagnostic tests (see above) and linking these to local resistance patterns and the development of algorithms to link resistance to clinical outcomes;
- bringing animal antibiotic usage patterns more into line with those used in human medicine (eg by restricting long term use in prophylaxis and growth promotion);
- review of improvements could be made in clinical trial methodology so that antibiotic trials do not simply demonstrate equivalence between the test agent and its comparator. This is currently a drawback of antibiotic clinical trial methodology. This could be addressed in improved phase IV clinical trial design to demonstrate real differences between antibiotics in bacterial eradication rates and clinical outcome; and
- redress the current technology gap in microbiology in the UK. There is a lack of trained people in the UK for pharmaceutical/antimicrobial research. Microbiology as a scientific discipline, has been underfunded in the UK, just as in the USA, for many years. The renaissance of interest in anti-infectives within pharmaceutical companies requires an enlightened funding attitude within the UK and Europe to redress this situation. Collaborative programmes such as Framework 5 are a step in the right direction.

The situation with regard to the development of anti-parasitic agents requires special consideration and for developments to be driven forward, there is a need for enlightened approaches in two areas:

- The first is that tropical parasitic diseases must be considered under the umbrella of orphan drug legislation, and within the bounds of Foresight initiatives in the EU. The EU legislation is essential to progress developments in this area.
- The UK Government should consider seeding grants (either absolute or returnable on the basis of time-limited royalties) to encourage compound development in these areas of low commercial return, but recognised global health importance.
- successful implementation of the above options will not occur without continued Government support for intellectual property protection and the constant adaptation of patent and copyright law to address new technology developments such as genomics, multiarray diagnostics and computer algorithms.

Memorandum by the Society for General Microbiology

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1. DEVELOPMENT OF ANTIMICROBIAL AGENTS

Since the first clinical applications of synthetic compounds in the 1910s and of penicillin in the 1940s a wide range of antimicrobial agents has been developed, initially towards bacteria but then also against protozoa, fungi and viruses (Greenwood, 1997). This report mainly deals with agents active against bacteria and viruses.

Antibiotics either kill or inhibit the growth of a microorganism in very small concentrations. Originally derived from secretions of other microorganisms (eg fungi, *Penicillium* spp etc), most antibiotics today are at least in part chemically synthesized.

2. MECHANISM OF ACTION OF ANTIMICROBIAL AGENTS

The mechanisms of actions of antibacterial agents relate to different compartments and steps of bacterial propagation (Greenwood, 1997):

- Cell wall biosynthesis (beta lactams, vancomycin).
- Proteins synthesis (chloramphenicol, tetracyclines, macrolides, aminoglycosides).
- Nucleic acid synthesis (quinolones, rifampicin, metronidazole).
- Intermediary metabolism (trimethoprim, sulphonamides).

Antifungal agents mainly act by destabilizing the fungal membranes (Greenwood, 1997).

Antiprotozoal agents affect different stages of the lifecycles of *Plasmodium*, *Leishmania*, and *Trypanosoma*.

Antivirals act at different stages of viral replication in the infected cell (Hirsch et al, 1996):

- Penetration, uncoating (amantadine).
- viral DNA synthesis (acyclovir and derivatives; foscarnet).
- viral RNA synthesis (nucleoside and non-nucleoside reverse transcriptase inhibitors).
- mRNA synthesis (ribavirin).
- Protein synthesis (interferon).
- Protein maturation (protease inhibitors, glycosylation inhibitors).

3. DEVELOPMENT OF RESISTANCE TO ANTIMICROBIAL AGENTS

A bacterium, originally sensitive to an antibiotic, can become resistant in several ways (Courvalin, 1996):

- It can mutate the target gene for the antibiotic so that the target is no longer inhibited when the antibiotic is present; or
- It can acquire a gene inactivating or hindering the antibiotic. Such genes have evolved as part of antibiotic biosynthesis pathways ensuring that the organism which produces the antibiotic is not killed during the production process (Davies, 1997). Resistance can also arise from genetic changes in transport mechanisms relating to antibiotics (Paulsen et al, 1996).

Once resistance has appeared it can spread among microorganisms in a number of ways:

- Naked DNA carrying the resistance gene can be transferred from one bacterium to another (transformation);
- DNA can be transferred as part of a virus (transduction);
- Two bacteria can fuse creating a cytoplasmic bridge across which DNA can move (conjugation).

Following transfer by either of these mechanisms, DNA carrying resistance gene(s) can establish itself in the new environment in several ways:

- It may "recombine" with host cell DNA in sites with "related" sequences, resulting in integration into host cell DNA in sites with similar sequences (homologous recombination);
- It may integrate into the DNA of a recipient cell in areas lacking related sequences (non-homologous recombination). Best known in this context is the existence of "jumping genes" (termed

transposable elements or transposons). these are independent genetic elements carrying genes within themselves allowing cutting (splicing) or unrelated (host cell) DNA; thus, they can insert themselves anywhere in the DNA of a cell they have just entered. These elements are most important for the emergence of new combinations of resistance genes (Quintiliani and Courvalin, 1994; Francois et al, 1997);

- The resistance gene may exist in the cell as part of a plasmid. Plasmids can multiply independently without having to become part of the bacterial chromosome; this removes the constraints of recombination and allows resistance to spread anywhere where the plasmids can survive and multiply. Thus plasmids provide the most promiscuous pathway for gene spread.

Some plasmids are very limited, while others are very broad in their host range (Salysers and Shoemaker, 1994). Examples for the latter are plasmids which can spread between very different species of gram-negative bacteria, eg *E. coli* (some of which are responsible for major cases of food poisoning) and *Pseudomonas aeruginosa* (frequently the cause of chronic lung infection and disease in cystic fibrosis patients). Some plasmids have even wider host ranges spanning filamentous bacteria like *Streptomyces* and even yeast (Pansegrau et al, 1994; Giebelhaus et al, 1996).

Some plasmid systems related to plasmids carrying bacterial resistance genes can promote fusion with plant cells (Lessl and Lanka, 1994), thus providing a gene delivery system which can act as natural vehicle for spreading genes from a natural environment into patients in both the community and hospitals. A deeper understanding of the delivery systems may allow to develop agents which might block gene transfer (Lanka and Wilkins, 1995; Haase and Lanka, 1997; Daugelavicius et al, 1997). Knowledge of gene sequences of these plasmids has allowed the design of reagents for plasmid detection in complex samples such as manure, soil, water (see below), and also in clinical samples (Pukall et al, 1996; Götz et al, 1996).

Similarly, plasmids are prevalent among gram-positive bacteria such as *Staphylococcus*, *Streptococcus* and *Enterococcus* multiplying by very simple mechanisms (rolling circle replication) and surviving and replicating in many gram-positive bacteria as well as being able to transfer to gram-negative bacteria. Although the outer surfaces of these different bacteria are very different, the genes are surprisingly able to function in their abnormal host. Staphylococcal plasmids have required all sorts of resistance determinants allowing them to survive in very hostile environments (eg in the presence of metal ions and of detergents; Skurray and Firth, 1997). Some transposable elements are self transmissible carrying their own conjugative transfer systems which allow them to spread readily between different groups of bacteria (Courvalin, 1994).

Genetic analysis of sequences of DNA adjacent to antibiotic resistance genes in chromosomes have revealed that there are unique integration units near promoter sites. These integration elements are known as "integrons" and function as recombinational "hot spots" for site-specific recombination events between largely nonhomologous sequences of DNA. The Integron itself provides a function to facilitate sequence-independent recombination; such sequences are often preserved at the 3' end of inserted antibiotic resistance genes (Cameron et al, 1986; Stokes and Hall, 1989; Hall and Collis, 1995). Integrons carrying multiple antibiotic resistance genes are widespread in bacteria isolated in hospitals (Jones et al, 1997).

Important antibiotics can be classified into the following groups (Multiple Authors in Mandell et al, 1995):

- Beta lactames (penicillin) and beta-lactamase resistant penicillins;
- cephalosporins;
- fusidic acid;
- aminoglycosides;
- tetracyclines;
- chloramphenicol;
- rifamycins;
- metronidazole;
- macrolides;
- glycopeptides;
- trimethoprim and sulfonamides;
- quinolones;
- nitrofurantoin;
- mupirocin;
- antimycobacterials; and
- antifungals.

Microbes have developed resistance against practically all these different groups of antimicrobial agents (Ameyes and Gemmell, 1997).

Measurements of antimicrobial resistance is carried out qualitatively by disc diffusion methods or semiquantitatively by E-tests. The E-test enables to estimate Minimum Inhibitory Concentrations (MICs)

directly. Breakpoint antibiotic susceptibility tests allowing to assess susceptibility, intermediate susceptibility or resistance at clearly defined end points (break points) (Shanson, 1997).

4. MECHANISMS OF RESISTANCE TO ANTIMICROBIAL AGENTS

At least eight mechanisms of antibiotic resistance in bacteria have been described. (Mayer et al, 1995):

- inactivation by enzymes (beta lactamases);
- alteration of bacterial membranes (eg loss of membrane proteins and mutations in membrane proteins, alteration of inner membrane permeability, decreased intracellular accumulation of antibiotic due to active efflux);
- alteration of ribosomal target sites;
- alteration of cell wall precursor targets;
- alteration of target enzymes (eg penicillin binding proteins);
- overproduction of target enzymes; and
- bypass of antibiotic inhibition (eg by changed substrate specificity circumventing the inhibition of an enzyme by an antibiotic).

Although the emergence of antibiotic-resistant bacteria has generally been correlated with the rise and fall of specific antibiotics used in clinical practice, the chain of causality is not always clear cut. Appropriate computerised surveillance of antibiotic resistance patterns of hospital isolates may allow rapid detection of the emergence of new types of resistance. Molecular techniques will enable confirmation of the presence of new genes in the environment, and this in turn may then be correlated with the phenotypic measures in the clinical microbiology laboratory. Utilisation of molecular techniques greatly augments surveillance data. The study of the genetics of antibiotic resistance, particularly the awareness of the great mobility of plasmids and transposons has led to the conclusion that ultimately each antibiotic used may alter the micro-environment providing selective advantage to resistant organisms as has been shown after the introduction of drugs like trimethoprim (Murray et al, 1985) and erythromycin (Seppala et al, 1992, 1996). The emergence of multiresistant enterococci as nosocomial pathogens is very menacing (Uttley et al, 1988; Moellering, 1992; Rubin et al, 1992; Karanfil et al, 1992; Livornese et al, 1992; Boyce et al, 1994).

5. THE EPIDEMIOLOGY OF DRUG-RESISTANT PATHOGENS

The epidemiology of resistance can be based on:

- (a) passive surveillance; or
- (b) active structured surveillance.

Most epidemiological data up to now are based on passive surveillance. However, structured surveillance programmes have started to be developed.

Surveys of the development of drug-resistance in bacteria have been conducted in various places, and a list of significant increases of resistance to antimicrobial agents has been compiled for a number of microorganisms (Table 1). In general, substantial increases in resistances have been observed. In detail, the major problems in bacteria are as described below:

(a) *Mycobacterium tuberculosis*

There is increasing evidence for the development of single drug resistance (against isoniazide (INH), rifampicin, ethambutol and streptomycin). This provides the rationale for multidrug combination therapy. However, small numbers of multidrug resistant isolates are being recorded and have the tendency to increase. Surveillance in the UK is by CDSC and Regional Mycobacterium Reference Laboratories in the PHLS MYCORNET scheme. Collaborating schemes are in place or under development in other European countries and the US. WHO have set up a global surveillance project.

- (b) Methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA are isolated particularly in hospitals, and in the UK the isolation rate is on a steep increase in secondary and tertiary referral hospitals since approximately three years. There seems to be linkage to areas of high antibiotic usage. MRSA prevalence in the community is at present low but measurable. So-called epidemic strains of MRSA (EMRSA) have emerged. Auditing of antibiotic prescribing practices in hospital and community is important.

Treatment of disease caused by MRSA is in most cases with glycopeptides (vancomycin, teicoplanin). Recently vancomycin-resistant staphylococci have been detected in Japan. There is the possibility of transmission of vancomycin resistance from enterococci (see below). Strict isolation protocols of MRSA carriers in hospitals (including temporary ward closures) have to be balanced with the interests of the public and the hospitals to keep waiting lists short. The costs for the determination of vancomycin levels in treated patients are steeply increasing.

- (c) Resistance in enterococci. Enterococci occur in the normal human gut, normally without causing disease, but being able to cause severe local and systemic disease in immunosuppressed patients (renal, bone marrow and liver transplant patients). Enterococci have intrinsic (natural) resistance to antimicrobials but can also gain resistance by acquisition of resistance genes on plasmids or transposons (see above; resistance against tetracycline, macrolides, chloramphenicol, trimethoprim). In 1988 glycopeptide resistant enterococci (GRE) were detected (Uttley et al, 1988; Leclercq et al, 1988). The origin of GRE is likely to be from the food chain. GREs were isolated from farm animals and raw meat, and indistinguishable isolates were obtained from turkeys and the farmers raising them (van den Bogaard et al, 1997). The use of avoparcin (a glycopeptide used as growth promoter in the poultry and pig rearing industry) is likely to have contributed to the emergence of GREs (likely to have been transmitted by transposon, TN1546). The prevalence of vancomycin resistant enterococci (VRE) in turkey flocks not receiving avoparcin was 8 per cent, as compared with 60 per cent in flocks fed avoparcin ($P < 0.001$, van den Bogaard et al, 1997). Infection and disease caused by GRE are difficult to treat. (For review see Leclercq and Courvalin, 1997; Landman and Quale, 1997).

It is important to study possible transfer of GRE transposons to other microbial organisms in the gut (gram-negative bacteria). The danger of transfer of vancomycin resistance to MRSAs is imminent and has already been accomplished on a staphylococcus in a laboratory (Noble et al, 1992).

- (d) Resistance in *Streptococcus pneumoniae*. There is increasing resistance to penicillin and erythromycin (Seppala et al, 1992, 1997), and multi-resistant strains begin to emerge. Clonal spread of resistant strains has been observed (Soares et al, 1993).
- (e) Gram-negative bacilli. Many antibiotic resistances in gram-negative bacteria are plasmid or transposon-mediated and transferable, allowing a wide dissemination amongst species (eg. the genes coding for "TEM" beta-lactamases). High resistances in Asian countries are possible due to uncontrolled use of antibiotics while relatively low rates in Scandinavia and in the UK are likely to be attributable to conservative antibiotic usage.

The overuse of antibiotics in food producing animals is a major cause of resistance in *Salmonella* spp in the UK. The introduction of apramycin in calf husbandry gave rise to resistance to the closely related gentamycin (Ward et al, 1990). Many cattle isolates of *Salmonella* spp. are multiresistant (Threlfall et al, 1993). In order to control the food chain, the comparison of phage types of *Salmonella typhimurium* isolates from man and domestic animals becomes more important (Wall et al, 1995; Ridley et al, 1996). An increasing incidence of infection with multiresistant *Salmonella typhimurium* DT104 has been established in cattle since 1990. This strain was found in other animals of the food chain and also in humans. The use of fluoroquinolones and trimethoprim in food of animals has contributed to the development of resistance in zoonotic salmonellas (Threlfall et al, 1996; Piddock, 1996).

Vero-cytotoxin producing *E. coli* 0157 (VTEC0157) is found in apparently healthy cattle as a reservoir. Transmission to man is via meat, yoghurt, cheese and vegetables. There is a rise in the percentage of drug-resistant strains in 1992-96, mainly in VTEC0157 of phage type 2 (Thomas et al, 1996), but multidrug resistance is rare at present.

Quinolone resistance has developed in *Campylobacter* after the introduction of fluoroquinolones into veterinary medicine (Endtz et al, 1991).

- (f) Resistant *Neisseriae*

Plasmid-mediated resistance of *Neisseria gonorrhoeae* to tetracycline is increasing since 1987. UK gonococcal antibiotic resistance is rising slowly due to introduction from abroad and the selection of less sensitive strains by underdosing.

There is a low, but increasing resistance of *Neisseria meningitidis* isolates against penicillin in the UK, however practically no resistance against rifampicin (the drug of choice).

- (g) *Clostridium difficile*

There is the clinical problem of selecting for growth of *Clostridium difficile* causing toxic enterocolitis in patients treated with antibiotics, due to the inherent resistance of this microorganism to penicillin and cephalosporins.

6. NATURAL BACKGROUND OF BACTERIAL ANTIBIOTIC RESISTANCE GENES IN THE ENVIRONMENT AND THE SIZE OF THE PROBLEM

The widespread use of antibiotics in human medicine and in animal husbandry has resulted in a rapid dissemination of antibiotic resistance genes among bacterial populations. The spread is favoured by the positioning of such genes on plasmids or transposons (see above). However, little is known about the evolution of antibiotic resistance mechanisms and the natural reservoir of antibiotic genes. The understanding of the prevalence and circulation of such genes in the environment helps to comprehend the size of the problem (van Elsas, 1992; Shanahan et al, 1994).

Antibiotic resistance is found in antibiotic-producing microorganisms isolated from soil which need the mechanism for self-protection (Huddleston et al, 1997). These resistance genes are usually clustered with antibiotic biosynthesis genes (Hopwood et al, 1995).

A strong correlation between the proportion of resistant bacterial populations, and the use of antibiotics for therapeutic or ergotropic purposes could be shown in several instances. Antibiotics can either be spread by anthropogenic input or via *in situ* production by soil, fungi, actinomycetes and other bacteria. Various antibiotics (chlorotetracycline, oxytetracycline, neomycin, streptomycin, tylosine, bacitracine) have been routinely added in the past to the feed to stimulate livestock growth (Hays, 1978). Until into the 1960s, medically relevant antibiotics have also been applied for the control of plant diseases (Chiou and Jones, 1991, 1993). Antibiotic resistance genes were found in plants and seemed to be completely homologous to those found in well known, clinically isolated plasmids conveying streptomycin/sulfonamides resistances (Chiou and Jones, 1993). Antibiotics are spread in the environment via municipal waste, manure, through waste from antibiotic production or after passage of the animal gut to enter manure (Nap et al, 1992). The occurrence and role of antibiotic production in specific soils is now well documented (Thomashow et al, 1990; Wellington et al, 1993).

Dissemination of antibiotic resistance genes in the environment will be either by clonal selection of resistant microorganisms due to selective pressure or by gene transfer via transformation, transduction or conjugation (see above). It is known that none of the transferable plasmids in pathogenic enterobacteria contained the antibiotic resistance genes in the pre-antibiotic era (Hughes and Datta, 1993). Thus, the evolution of antibiotic resistance plasmids seems to have occurred by insertion of new resistance elements into pre-existing plasmid pools. Whereas gene transfer frequencies in both soil and water environments seem to be low, higher frequency are possible under conditions of enhanced bacterial survival and activity (Götz and Smalla, 1997). Transfer of genes between many bacteria have been observed in the aquatic environment (Wellington and van Elsas, 1992).

Recent advances in the application of nucleic acid techniques has allowed new insights into the origin, evolution and dissemination of resistance genes (van Elsas, 1992). Most studies have been done with clinical bacterial isolates but there are now also some studies on the prevalence of such genes in environmental bacteria; tetracycline resistance in bacteria from pigs or food (Lee et al, 1993); kanamycin resistance in environmental bacteria (Leff et al, 1993; Smalla et al, 1993a); streptothricin (st) resistance in bacteria from different environments (Smalla et al, 1993b; Tschäpe, 1994); and vancomycin resistance in bacteria from sewage and poultry (Klare et al, 1995; Witte, 1997).

Trying to understand the complexity and interactions of the spread of antibiotic resistant genes in the environment has to ensure representative sampling strategies. This is hampered by the well known fact that only a small percentage of bacteria of the natural environment are accessible to traditional cultivation. Furthermore it is known that several gram-negative bacteria of importance for human disease (*Shigella*, *Salmonella*, *Campylobacter*, *E. coli*, *Vibrio cholerae* etc) enter the so-called "viable but non-culturable state" under environmental stress. The use of detection techniques based on the polymerase chain reaction (PCR) has allowed assessment of the prevalence of antibiotic resistance genes in bacterial communities including non-culturable bacteria (Smalla and van Elsas, 1995) as shown by the wide distribution of kanamycin resistance genes (*npt II*) and of transposon Tn5 in soils, manure slurries and river water (Smalla et al, 1993a). Another example is the presence of the streptothricin (st) acetyl transferase gene in the environment (Smalla et al, 1993b). The emergence and spread of st resistance in enteric bacteria as a consequence of the application of noursethricin as a feed additive in piggeries was traced in epidemiological studies (Tschäpe, 1994). These resistance genes have now reached a self transfer state as detected in pig faeces and manure (Tschäpe, 1994; Pukall et al, 1996). Gram-positive and gram-negative bacteria with the st resistance phenotype could be detected in all the habitat studies.

It is clear that the emergence of antibiotic resistance traits amongst bacteria in the clinical and veterinary environment has been favoured by strong selective pressure. In the open environment antibiotic resistance traits are omnipresent. In soil the potential for selection and transfer of such traits is not fully understood due to uncertainties about the extent of selective pressure.

7. RESISTANCE AGAINST ANTIVIRALS

Antivirals presently in use are mainly the following:

Compound	Active against
Amantadine	influenza A viruses
Ribavirin	respiratory syncytial virus
Ganciclovir	cytomegalovirus
Aciclovir, valaciclovir, famciclovir, and foscarnet	herpes viruses
Zidovudine, didanosine, zalcitabine, protease inhibitors	retroviruses (HIV)
Interferon	hepatitis B and C viruses

Interferon is a cellular protein synthesised in infected cells conveying the so-called "antiviral state" to a number of different viruses by interfering with their mRNA and protein synthesis. Interferon is not virus-but species-specific. There is the prospect of specific antivirals against hepatitis B and C viruses.

Viral resistances have been observed against most antivirals: aciclovir, ganciclovir and foscarnet, amantadine, zidovudine and protease inhibitors (Hammer and Inouye, 1997). Zidovudine resistance mutations have been shown to develop in a cumulative fashion (Larder, 1994).

Resistances emerge by mutations in the genes coding for the drug targets, eg thymidine kinase of HSV or reverse transcriptase of HIV. In RNA viruses drug resistances emerge within months. Any given population of HIVs consists of a mixture of subpopulations of genetically slightly different viruses, termed a "quasispecies". Drug-resistant mutants have been found in the quasispecies of patients *before* antiretroviral treatment, explaining the quick accumulation of drug-resistant mutants under antiretroviral treatment.

The clinical significance of antiviral resistance is in longterm: therapeutic or prophylactic treatment of HIV infected individuals or of transplant patients. The quick emergence of drug resistance of HIV upon monotherapy provides the rationale for the application of combination therapy (most frequently by two reverse transcriptase inhibitors and one protease inhibitor).

Drug resistant viruses can be transmitted (influenza A, HIV). The significance of such resistant strains for the epidemiology is still under study.

8. CONTROL MEASURES

The enormous ability of microorganisms to mutate towards drug resistance or to acquire drug resistance genes makes the establishment of effective control measures a daunting task. Such measures have been developed in various ways as briefly described below:

(a) Prescription and use of antibiotics.

As there is reasonable evidence that levels of usage of antibiotics are often linked with increased antibiotic resistance, tight prescription policies in the hospital environment make sense. There is evidence that restricted usage of antibiotics can be followed by a decrease in drug resistance (Seppala et al, 1997). However, it has to be considered that bacterial resistance genes may be introduced through the food chain or patients referred from institutions without such policies, and that therefore any benefit is achieved by considerable effort with major resource implications.

Antibiotic resistance data in isolates obtained from the community should be collated and communicated to General Practitioners thus facilitating rational use of antibiotics. The length of antibiotic treatment should be limited, and cases for prophylactic (mostly long-term) application of antibiotics be considered carefully. Some hospitals have established rotation policies for antibiotic usage.

(b) Hospital based control of infection

All NHS hospitals have an infection control team, headed by an Infection-Control-Doctor (ICD) who in most cases is a consultant medical microbiologist. The ICD is supported by Infection-Control-Nurses. Control of infection in the community is effected by Consultants for Communicable Disease Control (CCDC). Infection control consists of routine surveillance, investigation of incidents, concerted actions in containment measures and long-term improvements, eg. of wards and operation theatres. National nosocomial infections surveillance systems will allow the early recognition of new resistance patterns in hospital environments (Hughes and Tenover, 1997) and the development of rational algorithms for infection prevention (Goldmann and Huskins, 1997; Goldmann et al, 1997).

(c) The consultant medical microbiologist has various roles with regard to antibiotics and will ensure that:

- the diagnosis of infection is of high standard and improved;
- only relevant antibiotics and clinically significant isolates are tested for antibiotic resistance;
- the quality of testing is assured;
- reporting of antibiotic sensitivities is restricted;
- general and specialised policies of antibiotic usage are developed;
- audits on usage and policies are carried out; and
- resources for prospective hospital surveillance and quantitative testing as appropriate are provided.

(d) Guideline for use of antibiotics

Those relate to:

- antibacterial formularies and usage policies;
- monitoring of usage in humans;
- medical education;

- reducing risk of infection (see b); and
- monitoring usage of antibiotics in animals entering the food chain.

(e) The role of the General Practitioner

The General Practitioner can considerably contribute to the reduction of antibiotic resistance by:

- seeking and obtaining information on antibiotic resistance patterns in microbes isolated in the community;
- following clear indications of antibiotic usage; and
- collaborating with Medical Microbiologists.

(f) The role of Government

The insight that uncontrolled usage of antibiotics in animal husbandry has long term consequences for entry of drug-resistant microbes into the human population via the food chain, has in the past prompted legislation barring the use of antibiotics which are used in humans, as “growth promoters” in food animals. Their prophylactic use in animals was also discouraged. Only therapeutic applications remain acceptable (Helmuth and Protz, 1997). The balance between interests of the food-producing industry and those of the public to avoid exposure to multidrug-resistant microorganisms is easier to find if decisions are based on informed opinions. Therefore, prospective surveillance of antibiotic resistance patterns in human, animal and environmental microbial isolates should be supported and studies be encouraged in which such patterns are correlated with antibiotic usage and audits of policies of antibiotic usage (ASM Report, 1995; Hughes and Tenover, 1997). Data and activities of the Public Health Laboratory Service can play a particular role in this respect. More research is needed to determine the spread of pathogens in closed populations (hospitals, child care facilities, schools and food production facilities) and to develop rapid, reliable diagnostic techniques for detection of pathogens in clinical specimens, food stuffs and environmental specimens (ASM Report, 1995).

(g) The role of Industry

Industry has to find it commercially attractive to invest in the development of antimicrobial agents. This is not always the case. Industry clearly has an important function in helping to develop novel antimicrobial agents using rational and innovative strategies (see below section 9).

(h) The role of international collaboration in the EU and WHO frameworks

This role is eminent in existing epidemiological surveillance schemes for particular microbial pathogens to which surveillance of antibiotic resistance patterns is increasingly added. As national borders become more and more transparent and international travel widespread, international surveillance schemes are not an option any more but a necessity.

A useful synopsis of the different strategic approaches to limit the emergence and spread of drug-resistant microbes has been provided by Cohen and Tartasky (1997).

9. THE FUTURE OF ANTIBIOTICS, DRUG DEVELOPMENT AND MOLECULAR STRATEGY OF DRUG DESIGN

The growing incidence of antibiotic resistance in bacterial pathogens represents a major clinical and epidemiological problem (eg. increasing multidrug resistance in staphylococci (MRSA) and *Mycobacterium tuberculosis*; see above).

In the past, new families of antibacterial antibiotics were mainly discovered by random screening of collections of microbes isolated from the natural environment and of libraries of chemicals. For some time this approach allowed us to stay “one step ahead” of the evolution of clinical drug resistance (Glazer and Nikaido, 1995). However, more recently concentration of efforts on the modification of existing classes of antibiotics in conjunction with a decreasing rate of discovery of new antibiotics has lead to a diminution in options for treatment of infections with certain microbes. It should be appreciated that natural resistance mechanisms to antibiotics pre-existed in microbes (eg in producers of antibiotics) prior to the clinical use of antibiotics and thus effectively provided a “platform” from which antibiotic resistance (through transfer of resistance genes and selection, see above) emerged in bacterial pathogens. Approaches to overcome the drug resistance problem include:

1. Continued chemical modification of available antibiotics using considerable chemical structure knowledge to allow a rational approach to drug design (Glazer and Nikaido, 1995).
2. Generation of novel variants of specific antibiotic classes by genetic engineering techniques. For example, the polyketide antibiotics (erythromycin and others) can now be engineered in appropriate *Streptomyces* host/vector systems to yield novel antibiotics (McDaniel et al, 1993).
3. Targeted screening for novel classes of antimicrobials from environments not previously exploited (eg marine environments).
4. Identification of novel targets in pathogens. Such targets might allow the development of drugs to which microbes are unlikely to have any natural intrinsic resistance, thereby possibly avoiding, or slowing down, the emergence of clinical resistance.

Among the novel targets being considered are the following:

- Bacterial proteins involved in cell division (Addinall and Lutkenhaus, 1996; Hale and de Boer, 1997);
- Key steps in peptidoglycan biosynthesis. Some aspects of peptidoglycan synthesis can be interfered with by the well known beta-lactam antibiotics. Despite the emergence of multiple systems for beta-lactam resistance in bacterial pathogens it is hoped that a closer understanding of the biochemistry of all aspects of peptidoglycan biosynthesis could be exploited for designing novel chemical inhibitors;
- Surface proteins in gram-positive bacteria. Some surface proteins play important roles as signals in colonisation and virulence. Particular sequence motifs have been identified in some of them. More knowledge of the biochemistry of synthesis, targeting assembly of these molecules, may lead to the development of agents interfering with these processes (Schneewind et al, 1995);
- Bacterial elongation factors. Such factors are involved in the translation of messenger RNAs into proteins in the bacterial ribosomal machinery. Several natural antibiotics are known to interfere with the processes of translation (eg chloramphenicol, streptomycin, erythromycin, tetracyclin etc). It may be possible to exploit detailed structure-function information on bacterial elongation factors (eg EF-Tu) in order to identify inhibitors via high throughput screening and/or rational design (Landini et al, 1996);
- Bacterial sigma factors. Sigma are involved in controlling the specificity of transcription of subsets of bacterial genes by the cellular DNA-dependent RNA polymerase. The key role of various such factors in controlling bacterial gene expression (particularly virulence gene expression) make them potentially useful targets for inhibition (Brown and Soehnshein, 1996).
- Protein secretion pathways. Many bacterial pathogens secrete proteins which are key virulence factors (eg *Vibrio cholerae*, pathogenic *E. coli* strains and *Staphylococcus aureus*). Several distinct protein secretion pathways have been identified in bacterial pathogens (Pugsley, 1993; Salmond and Reeves, 1993; Cornelis and Wolf-Watz, 1997). Any drugs which might block any of these pathways are likely to have widespread utility.
- Drug efflux pumps. Efflux pumps are used physiologically in the natural control of metabolism of various cellular components. Some of these efflux pumps can also eliminate many antibacterial drugs, and thus the inhibition of the function of multidrug efflux pumps is a rational target for drug therapy (Nikaido et al, 1994);
- Quorum sensing systems. It has recently been found that some bacterial pathogens growing at high cell density produce diffusible signalling molecules which switch on or enhance the production of virulence factors. Interference in such signalling systems could be the basis of development of novel antibacterials (Robson et al, 1997; Swift et al, 1996).

As the genomes of more microbial pathogens are becoming completely sequenced and the functional analysis of these genomes progresses, possible chemotherapeutic intervention targets will be identified. Targets being expressed as essential steps in pathogenesis will be particularly interesting (Hensel et al, 1995).

These strategies involve considerable investment in fundamental molecular biological analysis of bacterial pathogens. The era in which adequate numbers of therapeutic agents were generated by mass screening programmes has passed. The identification of new antimicrobial agents will require a multifaceted approach using combinational chemistry, functional genomics and bioinformatics, rational drug design, structural biology, genetics and molecular biology.

10. ACKNOWLEDGEMENT

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Table 1
SIGNIFICANT INCREASE OF RESISTANCE TO ANTIMICROBIAL AGENTS
EXAMPLES OF THE UK AND ABROAD

<i>Bacterium</i>	<i>Resistance against</i>	<i>Degree of resistance</i>				<i>Source</i>
		<i>year</i>	<i>%</i>	<i>year</i>	<i>%</i>	
<i>M. tuberculosis</i>	Multidrug ^a	1981	0.6	1995	1.2	PHLS, UK ¹
<i>Staphylococcus (MRSA)</i>	Methicillin	1990	2.2	1996	13.7	PHLS, UK
<i>Enterococci</i>	Vancomycin	1989	0.4	1995	10.8	USA ²
<i>Str. pneumoniae</i>	Penicillin	1989	0.3	1995	2.9	PHLS, UK
	Erythromycin	1989	3.3	1995	10.9	
<i>Klebsiella</i>	Ceftazidime	1989	2.7	1994	5.7	PHLS, UK
	Ciprofloxacin	1989	2.9	1994	6.5	
<i>Enterobacter</i>	Ciprofloxacin	1989	1.9	1994	7.1	PHLS, UK
<i>Pseudomonas</i>	Ciprofloxacin	1984	4.7	1994	7.3	PHLS, UK
<i>Salmonella</i>	Multidrug ^b	1985	6	1996	> 70	PHLS, UK
<i>typhimurium</i>	Ciprofloxacin	1994	1	1996	12	

¹ PHLS "Antibiotic Resistance in England and Wales" Evidence presented to the House of Lords, 1997.

² McDonald and Jarvis (1997). *Curr. Opin. Infect. Dis.* 10, 304-309.

^a INH, Rifampicin, Ethambutol.

^b Ampicillin, Chloramphenicol, Sulphonamides, Tetracycline.

APPENDIX 1

REFERENCES

- Addinall SG and Lutkenhaus J (1996). FtsA is localized to the septum in an FtsZ—dependent manner. *J. Bacteriol.* 178, 7167-7172.
- Ameyes SGB and Gemmel CG (1997). Antibiotic resistance. *J. Med. Microbiol.* 46, 436-470.
- ASM (1995). Report of the ASM Task Force on Antibiotic Resistance. *Antimicrob. Ag. Chemother.* 39 (Suppl), S1-S23.
- Boyce JM, Opal SM, Chow JW et al (1994). Outbreak of multidrug-resistant *Enterococcus faecium* with transferable *vanB* class vancomycin resistance. *J. Clin. Microbiol.* 32, 1148-1153.
- Brown SW and Sonenshein AL (1996). Autogenous regulation of the *B. subtilis* *genRA* operon. *J. Bacteriol.* 178, 2450-2454.
- Cameron FH, Groot-Obbink DJ, Ackerman VP and Hall RM (1986). Nucleotide sequences of the AD (2") aminoglycoside adenylyl transferase determinant *aadB*. Evolutionary relationship of this region with those surrounding *aadA* in R-538-I and *dhFrII* in R388. *Nucleic Acids Res.* 14, 8625-8635.
- Chiou C-S and Jones AL (1991). The analysis of plasmid-mediated streptomycin resistance in *Erwinia Amylovora*. *Phytopathology* 81, 710-714.
- Chiou C-S and Jones AL (1993). Nucleotide sequence analysis of a transposon (Tn 5393) carrying streptomycin resistance genes in *Erwinia amylovora* and other Gram-negative bacteria. *J. Bacteriol.* 175, 732-740.
- Cohen FL and Tartasky D (1997). Microbial resistance to drug therapy: A review. *Amer. J. Infect. Control.* 25, 51-64.
- Cohen ML (1992). Epidemiology of drug resistance: implications for a post-antimicrobial era. *Science* 257: 1050-1055.
- Cornelis GR and Wolf-Watz H (1997). The *Yersinia* Yop virulon: a bacterial system for subverting eukaryotic cells. *Mol. Microbiol.* 23, 861-867.
- Courvalin P (1994). Transfer of antibiotic resistance genes between gram-positive and gram-negative bacteria. *Antimicrob. Ag. Chemother.* 38, 1447-1451.
- Courvalin P (1996). Evasion of antibiotic action by bacteria. *J. Antimicrob. Chemother.* 37, 855-869.
- Daugelavicius R, Bamford JKH, Grahm AM, Lanka E and Bamford DH (1997). The IncP plasmid encoded envelope-associated DNA transfer complex increases cell permeability. *J. Bacteriol.* 179, 5195-5205.

Davies JE (1997). Origins, acquisition and dissemination of antibiotic resistance determinants. *Ciba Found. Symp.* 207, 15-27.

Endtz HP, Ruijs GJ, Van Kluigeren B, Jansen WH, Van der Reyden T and Mouton RP (1991).

Quinolone resistance in *Campylobacter* from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *J. Antimicrob. Chemother.* 27, 199-208.

Fass RJ, Barnishan J and Ayers LW (1995). Emergence of bacterial resistance to imipenem and ciprofloxacin in a university hospital. *J. Antimicrob. Chemother.* 36, 343-353.

Francois B, Charles M and Courvalin P (1997). Conjugal transfer of tet(s) between strains of *Enterococcus faecalis* is associated with the exchange of large fragments of chromosomal DNA. *Microbiology* 143, 2145-2154.

Giebelhaus LA, Frost L, Lanka E, Gormley EP, Davies JE and Leshiw B (1996). The tra2 core of the P alpha plasmid RP4 is required for intergenic mating between *E. coli* and *Streptomyces lividans*. *J. Bacteriol.* 171, 6378-6381.

Glazer AN and Nikaido H (1995). *Microbiol Biotechnology. Fundamentals of Applied Microbiology*, pp 431-513, Freeman Publ., Basingstoke.

Goldmann DA and Huskins WC (1997). Control of nosocomial antimicrobial-resistant bacteria: A strategic priority for hospitals worldwide. *Clin. Infect. Dis* 24 (Suppl 1), S139-S145.

Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J and Martone WJ (1996). Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. *J. Amer. Med. Ass.* 275, 234-240.

Götz A, Pukall R, Smit E, Tietze E, Prager R, Tschäpe H, Vanelson JD and Smalla K (1996). Detection and characterization of broad host range plasmids in environmental bacteria by PCR. *Appl. Environm. Microbiol.* 62, 2621-2628.

Götz A and Smalla K (1997). Manure enhances plasmid mobilization and survival of *Pseudomonas putida* introduced into field soil. *Appl. Environm. Microbiol.* 63, 1980-1986.

Greenwood D (1997). Historical introduction and Modes of Action. In: *Antibiotic and Chemotherapy. Anti-Infective Agents and their Use in Therapy*, 7th edition, edited by F O'Grady, HP Lambert, RG Finch and D. Greenwood, p 2-9 and 10-22. Churchill Livingstone, New York etc.

Haase J and Lanka E (1997). A specific protease encoded by the conjugative DNA transfer systems of IncP and Ti plasmids is essential for pilus synthesis. *J. Bacteriol* 179, 5728-5735.

Hale CA and de Boer PAJ (1997). Direct binding of FtsZ to ZipA, an essential component of the septal ring structure that mediates cell division in *E. coli*. *Cell.* 88, 175-185.

Hall RM and Collis CM (1995). Mobile genetic cassettes and integrons: capture and spread of genes by site-specific recombination. *Mol. Microbiol.* 15, 593-600.

Hammer SM and Inouye RT (1997). Antiviral agents. In: *Clinical Virology*, edited by DD Richman RJ Whitley, and FG Hayden, pp 185-250. Churchill-Livingstone, New York etc.

Hays, VW (1978). The role of antibiotics in efficient livestock production. In: *Nutrition and Drug Interrelations*, edited by N Hatchcock and J Coon, pp 545-576, Academic Press, New York.

Helmuth R and Protz D (1997). How to modify conditions limiting resistance in bacteria in animals and other reservoirs. *Clin. Infect. Dis.* 24 (Suppl 1), S136-S138.

Hensel M, Shea JE, Gleeson C, Jones MD, Dalton E and Holden DW (1995). Simultaneous identification of bacterial virulence genes by negative selection. *Science* 269, 400-403.

Hirsch MS, Kaplan JC and D'Aquila RT (1996). Antiviral agents. In: *Fields Virology*, edited by BN Fields, DM Knipe, PM Howley et al, pp 431-466. Lippincott-Raven Publ., Philadelphia.

Hopwood D, Chater KF, and Bibb MJ (1995). Genetics of antibiotic production in *Streptomyces coelicolor* A3(2), a model streptomycete. In: *Genetics and Biochemistry of Antibiotic Production*, edited by LC Vining and C Stuttard, pp 65-102; Butterworth-Heinemann, Boston.

Huddleston AS, Cresswell N, Neves MCP, Beringer JE, C Baumberg S, Thomas DI, and Wellington EMH. (1997). Molecular detection of streptomycin-producing Streptomycetes in Brazilian soils. *Appl. Environm. Microbiol.* 63, 1288-1297.

Hughes JM and Tenover FC (1997). Approaches to limiting emergence of antimicrobial resistance in bacteria in human populations. *Clin. Infect. Dis.* 24 (Suppl 1), S131-S135.

Hughes VM and Datta N (1983). Conjugative plasmids in bacteria of the "pre-antibiotic" era, *Nature*, 302, 725-726.

Jones ME, Peters E, Weersnik AM, Fluit A and Verhoef J (1997). Widespread occurrence of integrons causing multiple antibiotic resistance in bacteria. *Lancet* 349, 1742-1743.

- Karanfil LV, Murphy M, Josephson A et al (1992). A cluster of vancomycin-resistant *Enterococcus faecium* in an intensive care unit. *Infect. Control Hosp. Epidemiol.* 13, 195-200.
- Klare I, Heier H, Claus H and Witte W (1995). *vanA*-mediated high-level glycopeptide resistance in *Enterococcus faecium* from animal husbandry. *FEMS Microbiol. Lett.* 125, 165-172.
- Landini P, Soffientini A, Monti F, Lociuo S, Marzorati E and Islam K (1996). Antibiotics MDL 62,879 and kirromycin bind to distinct and independent sites of elongation factor Tu (EF-Tu). *Biochemistry* 35, 15288-15294.
- Landman D and Quale JM (1997). Management of infections due to resistant enterococci: a review of therapeutic options. *J. Antimicrob. Chemother.* 40, 161-170.
- Lanka E and Wilkins BM (1995). DNA processing reactions in bacterial conjugation. *Ann. Rev. Biochem.* 64, 141-169.
- Larder BA (1994). Interaction between drug resistance mutations in human immunodeficiency virus type 1 reverse transcriptase. *J. Gen. Virol.* 75, 951-957.
- Leclercq R and Courvalin P (1997). Resistance to glycopeptides in enterococci. *Clin. Infect. Dis.* 24, 545-556.
- Leclercq R, Derlot E, Duval J and Courvalin P (1988). Plasmid-mediated resistance to vancomycin and teichoplanin in *Enterococcus faecium*. *N. Engl. J. Med.* 319, 157-161.
- Lee CY, Langlois BE and Dawson KA (1993). Detection of tetracycline resistance determinants in pig isolates from three herds with different histories of antimicrobial agent exposure. *Appl. Environm. Microbiol.* 59, 1467-1472.
- Leff LG, Dana JR, McArthur JV and Shimkets IJ (1993). Detection of Tn5-like sequences in kanamycin-resistant stream bacteria and environmental DNA. *Appl. Environm. Microbiol.* 59, 417-421.
- Lessl M, and Lanka E (1994). Common mechanisms in bacterial conjugation and Ti-mediated T-DNA transfer to plant cells. *Cell* 77, 321-324.
- Livornese LL, Dias S, Samel C et al (1992). Hospital-acquired infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. *Ann. Intern. Med.* 117, 112-116.
- Mandell GL, Bennett JE and Dolin R (Eds). *Principles and Practice of Infectious Diseases*, Churchill-Livingstone, New York etc.
- Mayer KH, Opal SM and Medeiros AA (1995). Mechanisms of antibiotic resistance. In: *Principles and Practice of Infectious Diseases*, edited by G. L. Mandell, J. E. Bennett and R. Dolin, pp 212-225. Churchill Livingstone, New York etc.
- McDaniel R, Ebert-Khosla S, Hopwood DA and Khosla C (1993). Engineered biosynthesis of novel polyketides. *Science* 262, 1546-1550.
- Moellering RC (1992). Emergence of *Enterococcus* as a significant pathogen. *Clin. Infect. Dis.* 14, 1173-1178.
- Multiple Authors (1995). Anti-infective therapy, Section E in: *Principles and Practice of Infectious Diseases*, edited by GL Mandell, JE Bennett and R Dolin, pp 199-528. Churchill Livingstone, New York etc.
- Murray BE, Alvarado T and Kim KH (1985). Increasing resistance to trimethoprim-sulfa-methoxazole among isolates of *Escherichia coli* in developing countries. *J. Infect. Dis.* 152, 1107-1113.
- Nap J-P, Bijvoet J and Stiekema W (1992). Biosafety of Kanamycin-resistant transgenic plants. *Transgen. Res.* 1, 239-249.
- Nikaido H (1994). Prevention of drug access to target: resistance mechanisms in bacteria based on permeability barriers and active efflux. *Science* 264, 388-393.
- Noble WC, Virani Z and Cree RGA (1992). Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTL 12201 to *Staphylococcus aureus*. *FEMS Microbiol. Lett* 93, 195-198.
- Pansegau W, Lanka E, Barth P, Figurski DH, Guiney D, Haas D, Helinski D, Schwab H, Stanisich V and Thomas C (1994). Complete nucleotide sequence of Birmingham IncP alpha plasmids. Compilation and comparative analysis. *J. Mol. Biol.* 239, 623-663.
- Paulsen IT, Brown MH, and Skurray RA (1996). Proton-dependent multidrug efflux systems. *Microbiol. Rev.* 60, 575-596.
- Piddock LJV (1996). Does the use of antimicrobial agents in veterinary medicine and animal husbandry select antibiotic-resistant bacteria that infect man and compromise antimicrobial chemotherapy? *J. Antimicrob. Chemother.* 38, 1-3.
- Pillay D and Geddes AM (1996). Antiviral drug resistance. *Brit Med J* 313, 503-504.
- Pugsley AP (1993). The complete general secretory pathway in gram-negative bacteria. *Microbiol Rev* 57, 50-108.
- Pukall R, Tschäpe H, and Smalla K (1996). Monitoring the spread of broad host and narrow host range plasmids in soil microcosms. *FEMS Microbiol Ecol* 20, 53-66.

Quintiliani R, and Courvalin P (1994). Conjugal transfer of the vancomycin resistance determinant between enterococci involves the movement of large genetic elements from chromosome to chromosome. *FEMS Microbiol Lett* 119, 359-363.

Ridley AM, Punia P, Ward LR, Rowe B and Threlfall EJ (1996). Plasmid characterization and pulsed field electrophoretic analysis demonstrate that ampicillin-resistant strains of *Salmonella enteritidis* phage type 6a are derived from *S. enteritidis* phage type 4. *J Appl Bacteriol* 81, 613-618.

Robson N, Cox ARJ, McGowan SJ, Bycroft BW and Salmond GPC (1997). Bacterial N-acyl homoserin lactone-dependent signalling and its potential biotechnological applications. *Trends Biotechnol* 15, 458-464.

Rubin LG, Tucci V, Cercenado E et al (1992). Vancomycin resistant *Enterococcus faecium* in hospitalized children. *Infect Control Hosp Epidemiol* 13, 700-705.

Salmond GPC and Reeves PR (1993). Membrane traffic wardens and protein secretion in gram-negative bacteria. *Trends Biochem Sci* 18, 7-12.

Salyers AA and Shoemaker NB (1994). Broad host range gene transfer: plasmids and conjugative transposons. *FEMS Microbiol Ecol* 15, 15-22.

Schneewind O, Fowler A and Faull KF (1995). Structure of the cell wall anchor of surface proteins in *Staphylococcus aureus*. *Science* 268, 103-106.

Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, Huovinen P and The Finnish Study Group for Antimicrobial Resistance (1997). The effects of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *New Engl. J. Med.* 337, 441-446.

Seppala H, Nissinen A, Jarvinen H et al (1992). Resistance to erythromycin in group A streptococci. *N. Engl. J. Med.* 326, 292-297.

Shanahan PMA, Thomson CJ and Amyes SGB (1994). The global impact of antibiotic-resistant bacteria: their sources and reservoirs. *Rev. Med. Microbiol.* 5, 174-182.

Shanson DC (1997). Laboratory control of antimicrobial therapy. In: *Antibiotic and Chemotherapy. Anti-Infective Agents and their Use in Therapy*, 7th edition, edited by F O'Grady, HP Lambert, RG Finch and D Greenwood, pp136-143. Churchill Livingstone New York etc.

Skurray RA and Firth N (1997). Molecular evolution of multiply antibiotic resistance *Staphylococci*. *Ciba Found Sump* 207, 167-183.

Smalla K and van Elsas JD (1995). Application of the PCR for detection of antibiotics resistance genes in environmental samples. In: *Nucleic Acids in the Environment* (Trevors, JT and van Elsas, JD, eds), pp241-256, Springer-Verlag Berlin, Heidelberg, New York.

Smalla K, Van Overbeek LS, Pukall R and Van Elsas JD (1993a). Prevalence of *nptII* and Tn5 in kanamycin-resistant bacteria from different environments. *FEMS Microbiol Ecol* 13, 47-58.

Smalla K, Prager R, Iseemann M, Pukall R, Tietze E, van Elsas JD and Tschäpe H (1993b). Distribution of streptothricin acetyltransferase encoding determinants among environmental bacteria. *Molec Ecol* 2, 27-33.

Soares S, Kristinsson KG, Musser JM and Tomasz A (1993). Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *J Infect Dis* 168, 158-163.

Stokes HW and Hall RM (1989). A novel family of potentially mobile DNA elements encoding site-specific gene integration functions. *Integrans Mol Microbiol* 3, 1669-1683.

Swift S, Throup JP, Williams P, Salmond GPC and Stewart GSAB (1996). Quorum sensing: a population density component in the determination of bacterial phenotype. *Trends Biochem Sci* 21, 214-219.

Tenover FC and Hughes JM (1996). The challenges of emerging infectious diseases: Development and spread of multiple-resistant bacterial pathogens. *J Amer Med Ass* 275, 300-304.

Thomas A, Cheasty T, Frost JA et al (1996). Vero-cytotoxin producing *E. coli* serogroup O157, associated with human infections in England and Wales, 1992-94. *Epidemiol Infect* 117, 1-10.

Thomashow LS, Weller DM, Bonsall RF and Pierson III IS (1990). Production of the antibiotic phenazine-1-carboxylic acid by fluorescent *Pseudomonas* species in the rhizosphere of wheat. *Appl Environm Microbiol* 56, 908-912.

Thomson CJ and Amyes SGB (1993). Molecular epidemiology of the plasmid-encoded TEM-1 β -lactamase in Scotland. *Epidemiol Infect* 110, 117-125.

Threlfall EJ, Frost JA, Ward LR and Rowe B (1996). Increasing spectrum of resistance in multiresistant *Salmonella typhimurium*. *Lancet* 347, 1053-1054.

Threlfall EJ, Rowe B and Ward LR (1993). A comparison of multiple drug resistance in salmonellas from humans and food animals in England and Wales, 1981-1990. *Epidemiol Infect* 111, 189-197.

Tschäpe H (1994). The spread of plasmids as a function of bacterial adaptability. *FEMS Microbiol Ecol* 15, 23-32.

Uttley AHC, Collins CH, Naidoo J and George RC (1988). Vancomycin-resistant enterococci. *Lancet* I, 57-58.

Van den Bogaard AE, Jensen LB and Stobberingh EE (1997). Vancomycin-resistant 37 enterococci in turkeys and farmers. *N Engl J Med* 337, 1558-1559.

Van Elsas JD (1992). Antibiotic resistance gene transfer in the environment: an overview. In: *Genetic Interaction among Microorganisms in the Natural Environment*, edited by EMH Wellington and JD van Elsas, pp17-39, Pergamon Press, Oxford.

Wall PG, Morgan D, Lauder K, Griffin M, Threlfall EJ, Ward LR and Rowe B (1995). Transmission of multi-resistant *Salmonella typhimurium* from cattle to man. *Vet Rec* 136, 591-592.

Ward LR, Threlfall EJ and Rowe B (1990). Multiple drug resistance in salmonellas isolated from humans in England and Wales: a comparison of 1981 with 1988. *J Clin Path* 43, 563-566.

Wellington EMH, Marsh P, Toth I, Cresswell N, Huddleston L and Schilhabel MB (1993). The selective effects of antibiotics in soil. In: *Trends in Microbial. Ecology*, edited by R Guerreo and C Pedrós-Aliós, pp 331-336. Spanish Society for Microbiology, Barcelona.

Wellington EMH and Van Elsas JD (1992). *Genetic Interactions among Microorganisms in the Natural Environment*. Pergamon Press, Oxford.

Witte W (1997). Impact of antibiotics use in animal feeding resistance of bacterial pathogens in humans. In: *Antibiotic Resistance: Origins, Evolution, Selection and Spread*. Ciba Foundation Symposium 207, 61-75. Wiley & Sons, Chichester etc.

APPENDIX 2

THE SOCIETY FOR GENERAL MICROBIOLOGY

"to advance the art and science of microbiology"

The Society for General Microbiology (SGM) was founded in 1945 and is now the largest microbiological society in Europe. It has over 5,400 members of whom about two-thirds are resident in the UK. The remainder reside in more than 60 countries throughout the world. Almost all full members are qualified to doctoral or higher level; there are 1,000 postgraduate student members.

The Society provides a common meeting ground for scientists working in academic centres and in a number of fields with applications in microbiology (medicine, veterinary medicine, pharmaceuticals, numerous industries, agriculture, the environment and education). The majority of Society members are employees of universities, research institutes, health services, government agencies and companies varying from small to multinational.

The science of microbiology covers a great diversity of infectious agents: disease-related molecular structures such as prions, and viruses, bacteria, fungi, protozoa and algae. Microbes are of crucial importance in a number of processes affecting all life on Earth; the cause and control of disease, fertility of soils and aquatic environments, decay and biodegradation of waste materials and dead biomass, fermentation and bioprocessing steps in pharmaceutical industries, and molecular biotechnology.

The Society's objective is to advance the art and science of microbiology. It does this by:

- Organising regular scientific meetings at centres throughout the UK and abroad, where microbiologists meet to hear and discuss the latest research findings. The largest meetings last 5-6 days and normally involve over 1,000 participants.
- Publishing three major international learned journals. *Microbiology*, *Journal of General Virology*, and *International Journal of Systematic Bacteriology*, as well as *SGM Symposium Series* books on current topics in microbiology.
- Keeping members informed of current developments in professional and scientific matters in microbiology, through publication of the *SGM Quarterly* and other means.
- Representing the science of microbiology on a number of biological and biomedical committees and organisations, in the UK and internationally, thereby exerting influence on science policy and education, regulatory affairs and international collaboration.

- Promoting microbiology as a career for young people by increasing awareness of microbiology in schools and the media, and providing financial support for young scientists to attend scientific meetings or training courses.

The Society is a Registered Charity (No 264017) and a Company Limited by Guarantee registered in England (No 1039582). It is governed by a Council drawn and elected from the membership; members of Council are directors of the company and trustees of the charity.

The Society's headquarter is at its freehold offices in Marlborough House, Basingstoke Road, Spencers Wood, Reading, Berkshire RG7 1AE, where it employs a staff of 30.

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APPENDIX 3

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December 1997

Memorandum by The Soil Association

The Soil Association is a registered charity established in 1946 to study and compare the long term impact of different farming methods. Since 1974 it has set and policed standards for organic food production¹ to provide practical encouragement for the development of alternative farming methods. Its aim is to promote awareness of the relationships between the way food is produced, human health and the environment. Increasingly it is seen as a consumer organisation, representing the interests of those who choose organic food.

1. The House of Lords Sub-Committee on Resistance to Antimicrobial Agents is aware of the extent to which the antibiotics² used in livestock production may be implicated in the growing incidence of antibiotic resistance³. We realise this aspect is not the primary focus of the Committee's work, however, we wish to

¹For the Soil Association standards on antibiotic use in livestock production see Appendix I

²Throughout this paper we use the term "antibiotic" to include both the true and synthetic antibiotics plus other antibacterial drug. This paper does not, however, consider the issue of resistance to other antimicrobial substances.

³Select Committee on Science and Technology Sub-Committee 1, Call for Evidence.

present evidence relating to inadequacies in the current regulatory structures for veterinary medicines in the UK, which falls outside the remit of other committees considering this topic.

2. In particular we wish to draw attention to:

- inadequacies in the mechanisms for regulating the use of antibiotics in agriculture, notably short comings in the licensing and review procedures with particular reference to the development and spread of antibiotic resistance;
- the shortsightedness of past administrations in rejecting (or failing to act upon) recommendations from advisory committees on antibiotic use in agriculture; and
- the susceptibility of the existing regulatory authority on antibiotic use in agriculture, the Veterinary Medicines Directorate (VMD), to lobbying from the pharmaceutical industry.

INADEQUACIES IN THE REGULATION OF ANTIBIOTICS IN AGRICULTURE

3. We believe there is evidence to suggest significant weaknesses in the mechanisms for regulating the agricultural use of antibiotics. While several government Ministries, departments, agencies and other bodies are involved with the licensing and control of veterinary medicines and aspects relating to their safety and safe use, no single agency or division of the Ministry of Agriculture would appear to have prime responsibility in relation to monitoring and controlling the development of antibiotic resistance due to:

- mutations assisted by selection pressure arising as a result of the widespread use of antibiotics at low concentrations in animal feeds;

and the spread of drug-resistance between bacterial species and strains affecting farm animals and from these species and strains affecting the human population, due to:

- cross-resistance between related antibiotics; and
- the phenomenon of transferable (infectious) drug-resistance⁴.

In addition to the obvious involvements of the Ministry of Agriculture, Fisheries and Food and the slight involvement of the Department of Health;

- licensing and residue monitoring are carried out by the Veterinary Medicines Directorate. This was established as an executive agency of the Ministry of Agriculture, Fisheries and Food in 1990. Its purpose is:

"To fulfil the functions of Ministers in relation to veterinary medicines and medicated feedstuffs under the Medicines Acts 1968 and 1971 and relevant European Community Directives and in relation to residues in meat and animal products under the Food Safety Act 1990." (VMD Framework Document 1995)

- monitoring and research relating to pathogenic organisms is undertaken by the Veterinary Laboratories Agency (VLA)⁵;
- a significant amount of research relating to antibiotic use in agriculture, some with particular reference to transferable antibiotic resistance, is carried out by the Public Health Laboratory Service;
- policing of prescriptions and the incorporation of antibiotics in livestock feed is monitored by the Royal Pharmaceutical Society of Great Britain; and
- the monitoring of veterinary medicines use on farms is undertaken by the State Veterinary Service, animal health officers, practising veterinary surgeons and recently also by trading standards officers.

4. The monitoring of antibiotic residues is a major aspect of the VMD's remit and is overseen by the Advisory Committee on Veterinary Residues. Reports are published both quarterly and annually and there are full backup services and facilities. At £3.7 million the budget for this activity accounts for 44 per cent of the VMD's total income and a substantial part of its work load.⁶ In contrast there is no mention within the terms of reference of the VMD to monitoring or controlling the development and spread of antibiotic resistance arising from the use of veterinary medicines. Efficiency within the VMD appears to have been the prime concern of Ministers in recent years (Waldergrave 1995) and one can understand an executive agency not allocating funds for work outside its key remit when it is not specifically instructed to do so. The VMD and the VLA both have only a passing interest in this area. In the case of the VMD this is through the Veterinary Products Committee (VPC) which keeps the issue of antibiotic resistance "under review" (Jones 1997). However, no specific resources are allocated to this area and the issue has a very low priority⁷. As recently as 1995 the VPC reviewed its policy in relation to antibiotic resistance and concluded that no change was required (Jones 1997). While the VLA undertakes research and monitors the incidence of pathogenic organisms affecting farm animals (including drug-resistant strains), and cases of reduced susceptibility to

⁴Transferable drug resistance is particularly significant among the Enterobacteriaceae and therefore relevant to the growing incidence of drug-resistant strains of food poisoning organisms. It was first identified in Japan in 1959 Watanabe (1963).

⁵Formerly the Central Veterinary Laboratories.

⁶Income for the year to 31 March 1997 was £8.46m. Of this £2.611m derived from statutory residue monitoring and £1.109m from non-statutory monitoring. Source VMD Income and Expenditure Accounts for the year to 31 March 1997.

⁷Total VMD expenditure on the VPC for all aspects of its work was £71,000 in the year to 31 March 1997.

antibiotics in farm animals can be reported to the VMD under its Suspected Adverse Reactions Scheme, the issues relating to drug resistance in farm animals with reference to its possible spread to the human population, appear notably lacking from the remit and concerns of both agencies.

5. It is surprising, and not immediately apparent, why such a high priority has come to be placed on monitoring antibiotic residues, while so little attention has been given to the issue of drug resistance. This is especially the case since the last and only major enquiry into antibiotic use in agriculture in the UK, undertaken by the Swann Committee in 1968/9, concluded in relation to antibiotic residues in food that:

"The limited evidence available to us does not suggest that antibiotic residues in food of animal origin pose any significant hazards to the consumer."

but in relation to transferable drug resistance:

"We have concluded that the administration of antibiotics to farm livestock, particularly at sub-therapeutic levels, poses certain hazards to human health... There has been a dramatic increase in the number of strains of enteric bacteria of animal origin which show resistance to... antibiotics... These strains are able to transmit this resistance to other bacteria. The resistance has resulted from the use of antibiotics for growth promotion and other purposes... There is incontrovertible evidence to show that man may commonly ingest enteric bacteria of animal origin... Some enteric organisms... are able to cause disease in man and... farm animals." (Swann Committee 1969, chapter XII).

6. To judge by the number of scientific papers it has published on this issue, the Public Health Laboratory Service (PHLS) on the other hand has taken a serious interest in the issue of drug resistance and its links with the agricultural use of antibiotics. For many years it has carried out research specifically in these areas and members of its staff have warned of the possible consequences of continuing with current policies. However, while the VMD and the VLA both formally advise agriculture Ministers on policy relating to veterinary medicines and public health, the PHLS has no such remit. It reports to and advises the Department of Health. While this seems only reasonable, since it is from there that it receives its funding, the effect of this is that the influence of the PHLS on veterinary medicines policy and licensing is either nonexistent or too far removed to have significant practical impact, despite the fact that a representative from the DOH attends meetings of the VPC.

7. It is also of note that the inclusion of antibiotics at sub-therapeutic doses does not leave residues in animal products which can be detected, even by today's highly sensitive methods. As such the entire surveillance programme of the VMD is effectively confined to antibiotics which are both classified as therapeutic and used at full therapeutic levels.

8. While it is obviously important to protect the public from antibiotic residues in food, it should be noted that the surveillance and monitoring of antibiotic residues carried out by the VMD has only a limited direct ability to protect public health, since food products are rarely withdrawn from sale and only a small percentage of animals are monitored. For those residues that are detected many times more are consumed by the public unknowingly. Monitoring antibiotic residues is carried out simply as a strategy to encourage livestock producers to observe the manufacturer's stated withdrawal times. There is no similar strategy in place for preventing the development and spread of drug-resistance, despite the fact that the issue is of potentially greater concern, since it poses a threat to large sections of society, rather than just to individuals.

9. In view of the policing role of the Royal Pharmaceutical Society in relation to medicated livestock feed, it is also of concern to us that the Society appears to have little awareness of the actual and potential contribution to the overall drug-resistance problem posed by the use of antibiotics in livestock production (Clements 1997).

10. We consider that these factors expose alarming failures in the regulatory systems for the control of antibiotics in agriculture.

FAILURE TO IMPLEMENT THE RECOMMENDATIONS OF ADVISORY COMMITTEES

11. The prevailing inadequacies in the mechanisms for regulating the agricultural use of antibiotics, including the lack of concerted and coordinated action by the various government departments and agencies, is largely due to the failure of government to implement a key recommendation of the 1969 Swann Committee. In Chapter XI of the Swann Report (Swann Committee 1969) the committee recommended that:

"One... committee should have overall responsibility for the whole field of the use of antibiotics and related substances whether in man, animals, food preservation, or for other purposes."

However, as Sir James Howie (1981), a former director of the PHLS, stated:

"In the event this fundamentally important Swann Recommendation was weakened. What emerged was... a Joint Sub-Committee for Antimicrobial Substances (JCAMS) under two parent committees: the Committee for Safety of Medicines (CSM) of the Department of Health and Social Security and the Veterinary Products Committee of the Ministry of Agriculture, Fisheries and Food."

12. The principal brief of the Swann Committee related to transferable drug resistance and despite the efforts of some industry-based scientists to undermine (see for example Anon, 1970, Mackinnon 1981) much of the committee's report is still relevant today. In relation to antibiotics the report states: "We are convinced

that one body must be able to look at all uses and their possible inter-relationships." The report further envisaged that in addition to advising on all aspects of antibiotic usage such a body would periodically review existing antibiotics to see if there should be "greater relaxation" or "more restrictive control".

13. By establishing an advisory sub-committee with two masters, rather than a single decision-making committee, government prevented several important functions envisaged by the Swann Committee from being carried out. The JCAMS was kept busy reviewing applications from manufacturers, but its advice was not always heeded and it was given no resources to examine aspects of applications which gave it cause for concern. It had no powers to review decisions on antibiotics made by other committees, nor even to review the use of previously licensed antibiotics. It was not even empowered to gather statistics on antibiotic usage, which had been another of the key Swann recommendations (Swann Committee 1969, paragraph 11.5). In addition the Safety of Medicines Committee rarely approached it. In 1980 the committee members felt so concerned that the situation was getting out of hand and that serious public health consequences might arise, that they put proposals for the committee's reform to the Ministers of Health and Agriculture. Instead of accepting these proposals, or even discussing them with the committee, the Ministers' reaction was immediately to abolish the committee. A move which was criticised in the medical, veterinary and farming press (Anon. 1981, Walton 1981a, Walton 1981b).

14. Sir James Howie, also commented (Howie 1981): "Is it not ironical that we now face another epidemic spread of salmonellas affecting calves and humans . . . indeed just such an episode as brought about the Swann Committee Report, one of whose main provisions is now being so unwisely set aside?"

15. It is difficult to avoid the conclusion that first, in not following the Swann recommendations more closely and second, in disbanding a committee made up of microbiologists eminently qualified to consider issues such as antibiotic cross resistance and transferable drug resistance, successive administrations acted unwisely, were cavalier in their approach to the issue of antibiotic resistance and were perhaps more influenced by the lobbying of pharmaceutical companies than they were concerned for the long term well being of the population.

SUSCEPTIBILITY OF THE VPC TO LOBBYING

16. There has been a long standing debate about the role of agricultural antibiotics in the development of resistance to antibiotics used in human medicine. Scientists from pharmaceutical companies and other industry representatives have tended to claim that the development of antibiotic resistance is either not significant or relates solely to the use of antibiotics in hospitals (eg Colegrave and Wesley 1995), whereas a number of academic microbiologists and many of those associated with public health and clinical medicine have tended to bring forth evidence to suggest that the problem is serious and that the use of antibiotics in agriculture, even since the adoption of some of the Swann Committee recommendations, is still a major source of concern (eg Linton 1977, Richmond 1981, Linton 1982, Witte 1997)⁹.

17. After disbanding the JCAMS government attempted to compensate for the loss of the committee by appointing two microbiologists to sit on the VPC and also invited representatives from the Department of Health, Department of the Environment and the Health and Safety Executive to attend meetings initially as observers, but more recently it appears, in an advisory capacity. However, commenting on this Walton (1981a) stated "Such a group has to be multi-disciplinary and therefore the simple strengthening of other committees by one or two members will not provide the breadth of specialised knowledge that is needed."

18. The fundamental problem that needed to be addressed was identified by Swann in 1969 and reiterated by Howie and Walton in 1981. As Walton (1981a) put it "What is really needed to cover those aspects of antibiotic usage indicated by the Swann Report is a small group of people with expertise in agriculture, public health, veterinary medicine, bacterial genetics and clinical hospital medicine. Such a group would need access to laboratory facilities, be provided with data on antibiotic usage and prevalence of antibiotic resistance". It may be of note that even today the list of VPC members appears only to include two microbiologists and still appears to be lacking representation from the area of clinical hospital medicine.

19. An additional problem is that when considering applications, members of the VPC are in the position of having to rely solely on data provided by manufacturers. This appears to place a faith in the integrity of the commercial world which few people would feel able to share. Can we really expect manufacturers to provide information which calls into question the safety of their products if they can possibly avoid it? There is in fact evidence that manufacturers do sometimes provide incomplete data from the trials they have conducted, or withhold subtle aspects of their own research, which might otherwise increase the likelihood of a particular application being rejected.

(Millstone et al 1994)¹⁰. Again this was one of the concerns of members of the abolished JAMCS. An editorial in the British Medical Journal (Anon. 1981) explained that the committee:

"Had no resources to commission field studies on a sufficient scale to monitor resistances or to have laboratory findings checked when applications to introduce a new antimicrobial agent left room for doubt about the validity of the conclusions presented."

⁹ See Appendix IV

¹⁰ Millstone and colleagues obtained and analysed raw data from Monsanto on trials the company was conducting with dairy cows being treated with bovine somatotrophin (BST). They compared this with published data which the company had submitted to the VPC in relation to its application to obtain a licence for BST in the UK and demonstrated that crucial information which showed an average 19 per cent increase in the Somatic Cell Count (or tendency towards mastitis) had not been made available to the VPC.

20. Members of the VPC are also provided with copies of dossiers from manufacturers applying to have products licensed. This information can be voluminous. Since members may have to consider several applications at each meeting it is sometimes impossible for them to do more than scan some of the papers with which they are provided. While members have the benefit of advice from the Medical and Scientific Panel this committee too appears to have little if any remit to consider the incidence and factors behind the rise and spread of antibiotic resistance¹¹. As such it can be deduced that members of the VPC sometimes have to rely heavily on advice from the VMD staff. However, since the licensing of antibiotics is a key part of the VMD's work, VMD staff have a considerable amount of contact with the pharmaceutical industry. As such it would not be surprising to find that they come to view the situation largely from the industry's point of view¹². This could, for example, be one reason why the British government was so out of step with other EU member states over the issue of avoparcin (Clover and Brown 1996). It is perhaps also of significance that the VMD is required under its remit from government to provide "high quality services to all its customers" (VMD 1995). Clearly the pharmaceutical industry is one of the VMD's principal customers and main sources of income. As such, consideration is needed to ensure there is also pressure on the VMD from consumers and their representatives, so that while fulfilling its obligation to the pharmaceutical industry it does not fail in its obligation to maintain "the safeguards of the licensing system" (VMD 1995).

CONSEQUENCES OF INADEQUATE REGULATION: THE EXAMPLE OF AVOPARCIN

21. The Swann Committee recognised the extent to which antibiotics fed routinely to farm animals at sub-therapeutic doses created a selective pressure for the emergence of drug-resistant bacteria, the potential for these to be transferred to man and the possibility that the resistance factors could then transfer to other bacterial species within the human gut. As a result the committee recommended that we should move away from the routine use of antibiotics in livestock production. However, the committee bowed to commercial pressure and accepted that there was, at that time, insufficient evidence to ban all antibiotics for growth promotion. It therefore accepted that if an antibiotic was not used for therapeutic purposes and would not compromise the efficacy of any therapeutic antibiotics, but was also effective as a growth promoter, it could be incorporated into animal feed without a veterinary prescription.

22. In 1969 the only antibiotic which fitted this description was zinc bacitracin, however, the Swann recommendations gave a clear signal to the pharmaceutical industry that it could invest in and develop growth promoting antibiotics if they complied with the criteria it had laid down.

23. The first such antibiotic to be licensed in the UK was spiramycin, a macrolide which shows cross-resistance with erythromycin (Anon. 1997d) and the second was avoparcin, a glycopeptide first licensed for use here in 1972 (Browning 1996) which came to be the most widely used growth promoting antibiotic in the UK. Avoparcin has come to public note since it was banned by the EU Commission on the recommendation of the Standing Committee on Feedstuffs from 1 April 1997 (Anon. 1997a), despite opposition from the British government (Browning 1997a).

24. While a detailed report in May 1996 from the Scientific Committee on Animal Nutrition (SCAN Report 1996) concluded there was no evidence to justify a ban on avoparcin, evidence has in fact been building for some time that some non-hospitalised people in the community have acquired VRE due to the use of avoparcin in livestock production (Bates 1994, Witte 1997, McDonald et al 1997, Anon 1997b).

25. It has taken 25 years to establish that avoparcin should never have been licensed as a growth promoting antibiotic, since it does not comply with the Swann recommendation, accepted by Ministers, that an antibiotic should only be licensed for growth promotion if it "Will not impair the efficacy of a prescribed therapeutic antibiotic . . . through the development of resistant strains of organisms" (Swann Committee 1969, paragraphs 9.11 to 9.13). Both avoparcin and spiramycin were licensed one year before the establishment of the JCAMS in 1973 and it seems likely that it was to these that an editorial in the British Medical Journal was principally referring when it bemoaned the fact that the JAMCS "had no powers to review the effects of antibiotics already approved" (Anon 1981). This was also a principal concern of Howie (1981) and Walton (1981a).

26. The current avoparcin ban (technically a suspension since it is to be reviewed) is due to concern about cross-resistance among the glycopeptides. However, soon after avoparcin was licensed serious concerns were raised by the Houghton Poultry Research Institute about the extent to which the feeding avoparcin and certain other antibiotics increasing the shedding of salmonella in poultry (Smith and Tucker 1975, 1978 and

¹¹ the terms of reference of the Medical and Scientific Panel are:

- to evaluate research currently available, and in progress, on OP dips in relation to possible human exposure;
- to advise on any additional work that may be needed to elucidate the potential long term effects on humans of OP sheep dips
- to advise on the suitability of any projects submitted for research and
- to report its findings to the Veterinary Products Committee, as its sub-committee (VPC 1996).

¹² It is felt that the UK may have been one of the Member States to which EU Agriculture Commissioner Franz Fischler was referring when "he expressed doubts that the various committees, notably the EU Standing Veterinary Committee, were sufficiently independent of national interests and pressure groups" (Cranford and Brown 1996). The remark was made in the context of the BSE crisis, but could, we feel, be equally relevant to the influence of the pharmaceutical industry.

1980). As a result a major supermarket stopped selling chickens fed avoparcin (Mudd 1977). Cyanamid, the company which initially developed and marketed avoparcin then reputedly spent a large amount of time and money reassuring the supermarket that the Houghton work was not replicated in field trials (Fussell, M 1981). It may perhaps, however, be relevant that no scientific paper was published in relation to this by Cyanamid, as far as we have been able to establish.

27. Critically, it would appear that JCAMS was prevented from reviewing the evidence of a possible link between avoparcin and salmonella in poultry. Since no regulatory action was taken here this aspect has remained largely unknown in the UK. Sweden, however, was also aware of this problem (Holmberg et al 1984) and the regulatory authorities there reacted in a very different way. Initially the use of avoparcin was banned and the drug was replaced in intensive poultry production by virginiamycin (Wierup 1997) the growth promoting antibiotic, to which most poultry producers have turned in the UK, since the avoparcin ban. Sweden then later banned all growth promoting antibiotics in 1986. While some commentators (eg Viaene 1977) have claimed that this led to an increase in the use of therapeutic antibiotics, the overall use of antibiotics in Sweden actually fell by 30 per cent between 1986 and 1988 and has not increased significantly since that time (Björnerot et al 1996).

28. Sweden, like the UK has experienced major outbreaks of salmonella food poisoning in the past, but the incidence is now extremely low and found in less than one per cent of all farm animal species and very rarely in cutting plants and retail outlets (Anon, 1995c). While this undoubtedly owes a great deal to the rigorous reporting and control methods employed in Sweden, the early ban on avoparcin and the ban on all growth promoting antibiotics in 1986 may also be significant¹³.

29. In the light of the major increase in salmonella that began in the UK a few years after the licensing of avoparcin and the continuing increase in drug-resistant salmonella that has come to affect all other animal species to which avoparcin has been fed, we feel this area is worthy of serious consideration. At the very least, one would have expected the UK regulatory authorities to have called for research to examine whether the phenomenon was in fact a significant factor in the increasing incidence of salmonella in poultry and if so whether a similar effect might also occur in other species¹⁴. That this was not done raises serious questions about the extent to which it is possible to have confidence in the regulation of antibiotics in UK livestock production. It further suggests possible lines of enquiry and research which might profitably be followed in relation to the drug-resistant strains of other bacterial organisms affecting both farm animals and man in recent years, and the factors behind their emergence.

RECOMMENDATIONS FROM THE SOIL ASSOCIATION

30. We recommend the need for an overall strategy to control the development and spread of antibiotic resistance. Such a strategy should have a number of components:

- a single multi-disciplinary committee (as envisaged by the Swann Committee) to oversee all aspects of antibiotic use in the UK;
- one ministerial department or agency to have overall responsibility for coordinating action to control the spread of drug resistance originating in farm animals;
- cross-departmental cooperation and coordination through all departments and agencies involved with the use of antibiotics, with veterinary education and with the development of agricultural policy;
- the review of existing research and the commissioning of new research to assist in the development of more integrated and health-oriented livestock production methods;
- the encouragement of a renewed interest in preventative veterinary medicine, with consideration given to taxing the use of routinely used antimicrobial products;
- full cooperation of the UK at an EU level. In this respect we urge that the British government should do all it can to speed the process of veterinary medicines harmonisation, always providing this can be achieved without compromises in relation to public safety; and
- full cooperation at an international level.

31. In particular we urge the adoption of the recommendations arising from the WHO meeting on The Medical Impact of the Use of Antimicrobials in Food Animals (Berlin October 1997) which stressed:

- (a) the need for national monitoring programmes to ascertain the prevalence of resistant bacteria in food-producing animal populations and animal-based food products including:
 - full collaboration between the medical, veterinary and agricultural sectors in establishing and conducting monitoring programmes:

¹³ See Appendix III

¹⁴ The avoparcin licence was extended in 1976 to allow it to be fed to cattle (Browning 1997b) including dairy cows and either at the same time, or soon afterwards to fattening sheep.

- the application of independent and standardised sampling and analytical techniques to allow for meaningful evaluation and comparison of results within monitoring programmes.
- (b) the need for review and modification of national policies on antibiotic use in agriculture, including:
 - improved enforcement policies to prevent the risk of antibiotics being used illicitly in agriculture;
 - specific education strategies to encourage the prudent use of antibiotics in animal husbandry by prescribers and farmers; and
 - the implementation of prescription and practice standards that ensure that antibiotics are not used as a substitute for good animal husbandry and to encourage the development of alternative, health-oriented management systems that reduce antibiotic use in farm animals.

32. In common with many other consumer groups we would like to see the WHO recommendations outlined above taken one step further and a complete ban imposed on the use of all antibiotics for growth promotion, as well as greater controls, and an overall reduction in the level of therapeutic antibiotics used for prophylaxis. This will only be possible if full support is given to the encouragement of alternative production systems and we would urge the House of Lords to draw attention to the way in which this process might be assisted by some redirection of agricultural subsidies through a reformed Common Agricultural Policy.

33. While some successful “models” of health-oriented production systems exist already, there are obstacles to their development which will need addressing:

- (a) it is likely that there will be increases in the cost of production of certain species (notably pigs and poultry) which may cause conflict with the World Trade Organisation and which need to be addressed in full cooperation with the other EU Member States; and
- (b) technical resources and the coordinated cooperation of regulators, researchers, veterinary professionals and agricultural establishments etc will be required in a concerted effort that can only be instigated by government.

34. In the light of past mistakes and in view of the potential consequences for human and animal medicine we believe it is no longer acceptable for licensing authorities to rely solely on information provided by manufacturers. We would suggest that with the prospect of the continuing harmonisation of EU veterinary medicines legislation the UK should work with other Member States to establish a centrally-funded body to carry out independent scientific studies in order to verify information from manufacturers and also, where necessary, to examine additional aspects.

35. We believe that consideration should be given to restructuring the Veterinary Products Committee to include not just consumer representatives (as has been muted) but specifically representatives from the Public Health Laboratory Service, the Communicable Disease Surveillance Unit and a bacteriologist involved with clinical hospital medicine. We also feel it advisable that further efforts are made to ensure as wide a cross section of scientists as possible within the committee structures of the Veterinary Medicines Directorate, so that decisions can be taken in the confidence that all possible adverse aspects have been considered in relation to the licensing of veterinary products.

Richard Young
Antibiotics Project Coordinator

12 January 1998

APPENDIX I

SOIL ASSOCIATION STANDARDS ON ANTIBIOTICS

The Soil Association sets and polices standards for organic food production through The Symbol Scheme which is registered with the United Kingdom Register of Organic Food Standards (UKROFS) as an Approved Organic Sector Body and is licensed to certify organic food production and processing under European Commission Regulation EEC No 2092/91.

Production Standards outline the principles and practices of organic agricultural systems which, within the economic constraints and technology of a particular time, promote:

- the production of high levels of nutritious food;
- the use of management practices which sustain soil health and fertility;
- high standards of animal welfare and contentment;
- the lowest practical levels of environmental pollution;
- minimal dependence on no-renewable forms of energy and the burning of fossil fuels; and
- enhancement of the landscape, wildlife and wildlife habitat.

In relation to the use of antibiotics the Soil Association Standards state:

“The use of antibiotics and some other conventional products may reduce natural immunity and, although providing rapid initial recovery, can leave an animal more prone to reinfection. They

should only be used under the advice of the nominated veterinary surgeon where effective alternative treatments are not available and where they are considered the best method of reducing suffering, saving life or restoring an animal to health.

5.711: *"Permitted: The use of antibiotics in clinical cases where no other remedy would be effective or after major trauma as a consequence of surgery or accident.*

5.712: *Prohibited (1) the prophylactic use of antibiotics on a herd or flock basis. (2) The prophylactic use of Dry Cow Therapy on a herd or flock basis."* (Anon 1997f).

APPENDIX II

EVIDENCE OF THE TRANSFER OF DRUG RESISTANCE FROM FARM ANIMALS TO THE HUMAN POPULATION

Drug resistant strains of *Campylobacter*, *Salmonella*, *Enterococci* and *E. coli* are known to have passed from animals to people. (WHO 1997c). Cross-resistance has also occurred with the glycopeptides (Bates et al 1994) the macrolides (Anon 1997d, Moore et al 1996), the lincosamides and streptogramins (Fussell 1981, Witte 1997e, Moore et al 1996) and with the fluoroquinolones (Thelfall et al 1996).

There is also a possibility that multiple drug-resistance could be transferred to other infectious diseases in certain situations. In particular the possibility that resistance to the glycopeptide Vancomycin could be transferred from Vancomycin-resistant enterococci (VRE) where it is now well established to Methicillin-resistant *Staphylococcus aureus* (MRSA) presents an alarming scenario with the potential for a major public health crisis (Anon. 1997e).

The increasing incidence of Vancomycin-resistant enterococci has been linked to the use of the related glycopeptide, avoparcin. While the use of avoparcin has been suspended throughout the EU since 1 April this year, the importation of meat, produced using avoparcin, from non-EU countries is still permitted and this provides an opportunity from the continuing flow of van-A genes (the effective mechanism of glycopeptide resistance) into the EU and the UK. It has been postulated that the importation of meat may be a factor in the rise of glycopeptide resistance in the USA, despite the fact that avoparcin has never been used there (Piddock, Witte and Levy, 1996).

It has further been suggested that the spread of resistance between avoparcin and VRE may be assisted by the fact that avoparcin is not pure and contains DNA from the producing organism, with the implication that this is the same organism from which vancomycin is derived (Davies 1997).

APPENDIX III

FURTHER EVIDENCE RELATING TO THE POSSIBLE INTERRELATIONSHIP BETWEEN THE USE OF ANTIBIOTICS IN FARM ANIMALS AND THE INCIDENCE OF SALMONELLA FOOD POISONING IN THE HUMAN POPULATION

It is widely known that the UK has seen a major increase in food poisoning cases in recent years. The problem of salmonellosis, for example, has been described as an "epidemic...both in man and farm animals" (Evans and Davies 1996).

It is now estimated that while the "reported" cases of food poisoning in Britain during 1997 will have exceeded 100,000 for the first time, the reality is that more than one million people will have been affected (Gilbert 1998), since it is estimated that only about 10 per cent of cases are reported. The number of cases of salmonella reported to the PHLS rose from about 5,000 in 1965 to over 25,000 in 1989 (Cooper et al 1993) and now stands at about 40,000 (Coghlan 1998).

Considerable effort has been put into controlling food poisoning bacteria in livestock production. After the outbreaks of *Salmonella enteritidis* in the mid-1980s, large numbers of poultry flocks were slaughtered; bacterial monitoring was introduced under the Poultry Breeding Flocks and Hatcheries Order 1993. There have been a number of MAFF research projects examining likely contributory factors such as the spread through contaminated feed and introduction via wild birds and farm cats, for example (Evans & Davies 1996). However, according to the most recent survey conducted by the PHLS, such strategy as there may be for controlling salmonella is far from effective, since one third of all frozen chickens sold in the UK are contaminated with salmonella (Coghlan 1998).

In addition to the increasing incidence of well established pathogenic strains and phage types of salmonella, a number of new strains and phage types have emerged in recent years. *Salmonella typhimurium* DT104 was first noted in 1982 but it is only in the last decade that it has emerged as clinically significant. More recently still *Salmonella hindmarsh* has affected a number of sheep flocks causing significant mortality and a small number of food poisoning cases in man. While the organism has been known for some time and is endemic in the environment in certain areas, this is the first time it is known to have become clinically pathogenic (Daniel et al 1997).

It should further be noted that some strains of salmonella have extended their infective range. For example, *Salmonella typhimurium* DT104 was initially only associated with cattle, but since 1993 it has become the principal strain of salmonella in sheep and poultry (Threlfall et al 1997) and is also found in pigs (Anon. 1996). In 1969 no sheep flocks in the UK had been infected with any pathogenic strain of salmonella (Swann Committee 1969) whereas it is now widespread, and it is only in the last few years that *Salmonella enteritidis* phage type 4, the most common salmonella infecting egg-laying hens has begun to affect broiler poultry too and as such provided an additional opportunity for transfer to humans.

Not only has the incidence and the number of pathogenic strains of salmonella increased, but these have become increasingly drug-resistant. In round figures the percentage of isolates sensitive to the 16 antibiotics normally used in evaluation tests has fallen from about 50 per cent in the early 1990s to about 10 per cent in the last two years. (Anon. 1996). In addition to this 94 per cent of samples sent to the Public Health Laboratory Service in London during 1995 were resistant to four or more antibiotics. Even more significantly 6 per cent were resistant to ciprofloxacin (due it is believed to the recent introduction into veterinary medicine of related fluoroquinolones such as enrofloxacin) and 27 per cent to trimethoprim, an important drug often used in combination with sulphonamides to treat respiratory and urinary infections in humans. In addition 13 per cent of cattle herds affected by *Salmonella typhimurium* DT104 have some cases of trimethoprim resistance. In contrast in 1973 and 1974, before the emergence of *Salmonella typhimurium* DT104, all 5,905 known strains of salmonella were sensitive to trimethoprim/sulphonamide (Soika et al 1977).

The transmission of some salmonella strains from animals to humans is well documented (eg Wall et al 1995) and concern over drug-resistant salmonella is of course not new (Anderson 1968, Threlfall et al 1980). It was for example a key factor behind the establishment of the Swann Committee in 1968. As such it is of note that the committee concluded:

"We agree that the outbreaks of infection due to Salmonella typhimurium phage type 29... include instances in which human disease and death resulted from multiple-resistant organisms which acquired their resistance through the use of antibiotics in animals" (Swann Committee 1969 paragraph 5.18).

Antibiotics are not normally used to treat salmonella infection in the human population. Most people recover from salmonella food poisoning without the need for antibiotic treatment, although they are essential in the case of typhoid, paratyphoid and on other occasions when salmonella infection becomes systemic (Swann Report 1969 Chapter IV). In contrast, therapeutic antibiotics are generally used to treat salmonella infections in farm animals (Wall 1997). Therapeutic antibiotics, including fluoroquinolones, are also used in attempts to eradicate salmonella infections from poultry flocks (Humbert et al 1997) and from pigs (Raemdonck et al 1994). Where the salmonella strain is sensitive to the antibiotic used some improvement will be achieved. We have insufficient evidence to comment on the success of this in relation to pigs, but the practice is, however, known to be unsuccessful as a way of eradicating salmonella in poultry flocks (Humbert et al 1997).

It is widely understood that the use of antibiotics in livestock production produces a selection pressure which can favour mutant strains, some of which are likely to be both pathogenic and antibiotic resistant (Swann Committee 1969, Chapter V, Levy 1997). In view of this it appears probable that despite any short term improvements achieved in intensive livestock systems in relation to salmonella disease levels, the widespread use of therapeutic antibiotics in an attempt to control salmonella, in fact, make the overall situation worse.

It would therefore appear that both the therapeutic use of antibiotics in livestock production, as detailed above, and the use of all, or some, antibiotics for growth promotion (as set out in paragraphs 21–29, above, "Consequences of Inadequate Regulation: The Example of Avoparcin") may be significant contributory factors in the considerable increase in the overall incidence of salmonella, the increase in drug resistance and the development of new strains or phage types associated with farm animals. Since salmonella is also one of the *Enterobacteriaceae* in which transferable drug resistance is known to occur and since many salmonella strains affect both humans and farm animals, it would appear that this particular area is long overdue for detailed research and that a more precautionary approach should be adopted until such research has been completed.

APPENDIX IV

CONTINUING EXCESSIVE USE OF ANTIBIOTICS IN UK AGRICULTURE

Linton (1977 and 1982) explained in detail why legislation, even after the adoption of many of the Swann Committee's recommendations, was still failing to halt the rise in drug-resistant bacteria passing from animals to people.

He pointed out that the separation between therapeutic and feed antibiotics as it was being practised, was largely an artificial one. The distinction is blurred by the fact that the use of most therapeutic antibiotics at sub-therapeutic levels has a significant growth promoting effect and their routine use is therefore to the commercial advantage of producers. There can also be therapeutic effects from the use of the growth promoting antibiotics (Hellig 1996, Mudd 1997).

The reality is that the therapeutic antibiotics have been prescribed for routine use, especially in pig and poultry feed during the last twenty years, in roughly the same way they were used in an unrestricted fashion prior to the Swann Committee's report. This is the case, for example, with oxytetracycline to which many enterobacteria and salmonella have become resistant (Avon. 1995b). The only substantial difference is that a small number of antibiotics are no longer used in this way and a wider range of antibiotics is generally available. However, this wider range includes many antibiotics closely related to important antibiotics used in human medicine and between which cross resistance can occur.

The total quantity of therapeutic antibiotics used in livestock feed fell sharply in the early 1970s immediately after the publication of the Swann Report, but started to rise again from 1974 and by 1977 was equal to the pre-Swann levels (Linton 1982). Since government does not gather statistics it is difficult to state what quantity of antibiotics is used at the present time. However, it is generally accepted that the usage has continued to increase since 1977. One example of this is that virtually all pigs and broiler poultry in the UK receive POM antibiotics during the early stages of life and either PML antibiotics or POM antibiotics in feed for the rest of their lives (Rain, 1977).

We see such use as excessive. We believe it is necessary to reduce the overall quantity of antibiotics used in this way. Since ill animals must of course be treated, the only way in which such reductions will be achieved is through substantial changes in management practices or the adoption of alternative approaches to livestock rearing.

REFERENCES

- Anderson ES. 1968. Drug Resistance in *Salmonella typhimurium* and its implications. *Brit Med J* 3: 333-339.
- Anon. 1970. The Swann Report—Dialogue in the Press. Compilation of press cuttings prepared by the Graham Cherry Organisation for Cyanamid.
- Anon. 1981. Death of a Quango. *Brit Me. J* 282: 1413-1414.
- Anon. 1995a. Review Amendment and Interpretation of the Framework Document. VMD Framework Document. *MAFF*. PB2041.
- Anon 1995b. Terramycin feed Supplements. Entry in *Handbook of Medicinal Feed Additives 1995-96*. Ed Mounsey AD, page 213-214. HGM Publications.
- Anon. 1995c. Swedish Salmonella Control Programmes For Live Animals, Eggs and Meat. National Veterinary Institute, Swedish Board of Agriculture, National Food Administration. Dnr 728/85. Saknr 2349.
- Anon. 1996. Salmonella in Livestock Production. Veterinary Laboratories Agency. *MAFF*.
- Anon. 1997a. Ban on the antibiotic "Avoparcin" in animal feed. EU press release IP/97/71 30 January 1997.
- Anon. 1997b. *New England Journal of Medicine*, 337: 1158, cited by Coghlan, A, *New Scientist* 6 December 1997 page 5.
- Anon. 1997c. World Health Organisation. Antibiotic Use in Food-Producing Animals Must Be Curtailed To Prevent Increased Resistance In Humans. WHO/73 Press Release 20 October 1997 Switzerland.
- Anon. 1997d. Tylosin and Spiromycin as feed additives. Influence on the efficacy of therapeutical macrolides. Report by the National Veterinary and Food Research Institute (EELA), the Republic of Finland.
- Anon. 1997e. Reduced Susceptibility of *Staphylococcus aureus* to Vancomycin. Centers for Disease Control and Prevention MMWR 11 July 1997.
- Anon. 1997f. Standards for Organic Food and Farming. The Soil Association. Revision 11.
- Bates J, Jordens Z and Griffith DT, 1994. Farm animals as a putative reservoir for vancomycin resistant enterococcal infection in man. *J Antimicrob. Chemother.* 34: 507-514.
- Björnerot L, Franklin A., and Tysén E, 1996. Usage of antibacterial and antiparasitic drugs in animals in Sweden between 1988 and 1993. *Vet. Rec.* 139:282-286.
- Browning, A 1996. Written answer to Parliamentary Question 464 from Martyn Jones MP. 13 December 1996.
- Browning, A 1997a. Written answer to Parliamentary Question 1208 concerning avoparcin, from Martyn Jones MP. 18 March 1997.
- Browning, A 1997b. Written answer to Parliamentary Question 1172 from Martyn Jones MP. 19 March 1997.
- Clements JA 1997. Personal Communication with Dr. John Clements, Head of Scientific and Technical Services, Royal Pharmaceutical Society.
- Clover C and Brown D 1996. Hospital fear brings ban on animal fed antibiotic. *Daily Telegraph* 21 December 1996, page 4.

- Coghlan A 1998. Is anything safe to eat? *New Scientist* 3 January 1998.
- Colgrave T, with Wesley T 1995. The Feed Additives Market. PJB Publications Ltd.
- Cooper GL, Venables RAJ, Nicholas GA, Cullen GA and Hormaaeche CE (1993). Further studies of the application of live *Salmonella enteritidis* araA vaccines in chickens. *Vet. Rec.* 133, 31-36.
- Cranford H and Brown D 1996. Brussels plans to set up safety agency. *Daily Telegraph* 16 December 1996, page 5.
- Daniel RG, Barrow P, Szmolleny G and Wood M. 1997. *Salmonella hindmarsh* infection in sheep and ponies. *Vet Rec* 141: 203.
- Davies JE. 1997. Discussion during symposium *Antibiotic resistance: origins, evolution, selection and spread*. Wiley Chichester (Ciba Foundation Symposium) 207: 72.
- Evans S and Davies R. (1996). Case control study of multiple-resistant *Salmonella typhimurium* DT104 infection of cattle in Great Britain, *Vet Rec* 139, 557-558.
- Fussell MH. (1981) Antibiotics as Growth Promoters. Proceedings of Symposium *Ten Years on From Swann* organised by the Association of Veterinarians in Industry.
- Gilbert R. 1998. Quoted in, Is anything safe to eat? *New Scientist* 3 January 1998.
- Hellig H. 1996. Interview on BBC Radio 4's Farming Today 20 December 1996.
- Holmberg T, Wierup M and Engström. 1984. The effect of Feeding Diets Containing Avoparcin and Monensin on the Occurrence of *Salmonella* in Caecum and Liver in Experimentally Infected Chickens. *Poultry Science* 63, 1144-1148.
- Howie J. 1981. The Situation in the UK—then and now. Proceedings of Symposium *Ten Years on From Swann* organised by the Association of Veterinarians in Industry.
- Humbert F, Carramiñana JJ, Lalande F and Salvat G. 1997. Bacteriological monitoring of *Salmonella enteritidis* carrier birds after decontamination using enrofloxacin, competitive exclusion and movement of birds. *Vet Rec* 141: 297-299.
- Jones RS. (1997). Letter from Professor R. S. Jones, President of the Royal College of Veterinary Surgeons to Mr Martyn Jones MP, 13 February 1997.
- Levy S. 1997. Antibiotic resistance: an ecological imbalance. *Antibiotic resistance: origins, evolution, selection and spread*. Wiley Chichester (Ciba Foundation Symposium) 207.
- Linton AH. 1997. Antibiotic resistance: The present situation reviewed, *Vet Rec* 100, 354-360.
- Linton AH. 1982. The Swann Report and its Impact, paper given at a conference on The Control of Antibiotic Resistant Bacteria, Academic Press.
- MacKinnon JD. 1981. The Use of Tylosin in Feed and Therapy—A Review. Proceedings of Symposium *Ten Years on From Swann* organised by the Association of Veterinarians in Industry.
- McDonald CL, Keuhnert MJ, Tenover FC and Jarvis WR. 1997. Vancomycin-Resistant Enterococci Outside the Health-Care Setting: Prevalence, Sources and Public Health Implications. *Emerging Infectious Diseases* 3: 311-317. Centre for Disease Control and Prevention Atlanta, USA.
- Millstone E, Brunner E and White I. 1994. Plagiarism or protecting public health? *Nature* 371: 647-648.
- Moore JE, Madden RH, Kerr JR, Wilson TS and Murphy PG. 1996. Erythromycin-resistant thermophilic *Campylobacter* species isolated from pigs. *Vet. Rec.* 138: 306-307.
- Mudd A. 1997. Personal communication with Dr. Tony Mudd, Roche Products Ltd.
- Piddock L, Witte W and Levy S. 1997. Discussion during symposium *Antibiotic resistance: origins, evolution, selection and spread*. Wiley Chichester (Ciba Foundation Symposium) 207: 72.
- Raemdonck DL, Tanner AC, Tolling ST and Michener SL. 1994. Antimicrobial susceptibility of *Actinobacillus pleuropneumoniae*, *Pasturella multocida* and *Salmonella choleraesuis* isolates from pigs. *Vet Rec* 134: 5-7.
- Raine H. 1997. Incorporation into animal feeds, paper presented at a conference on The Responsible Use of Medicines. Elanco, NOAH and the BVA, 29 October 1997.
- Richmond MH. 1981. Antibiotic Use and Resistance. Proceedings of Symposium *Ten Years on From Swann* organised by the Association of Veterinarians in Industry.
- SCAN Report 1996. Report of the Scientific Committee for Animal Nutrition (SCAN) on the possible risk for humans on the use of avoparcin as a feed additive. VI/6474/96-rev1.
- Smith HW and Tucker. 1975. The effect of feeding diets containing permitted antibiotics on the faecal excretion of *Salmonella typhimurium* by experimentally infected chickens. *J Hyg Camb* 75, 293-301.
- Smith HW and Tucker. 1978. The effect of antimicrobial feed additives on the colonisation of the alimentary tract of chickens by *Salmonella typhimurium*. *J Hyg Camb* 80, 217-231.

Smith HW and Tucker. 1980. Further observations on the effect of feeding diets containing avoparcin, bacitracin and sodium arsenilate on the colonisation of the alimentary tract of poultry by *Salmonella typhimurium* *J Hyg Camb* 84, 137-150.

Sojka WH, Wray C and Hudson EB. (1977). *Brit Vet J* 133, 292.

Swann Committee 1969. Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine (Swann Committee Report). HMSO, London.

Threlfall EJ, Ward LR, Ashley AS and Rowe B. 1980. Plasmid-encoded trimethoprim resistance in multiresistant *Salmonella typhimurium* phage types 204 and 193 in Britain. *British Medical Journal* 17 May 1980 pages 1210-1211.

Threlfall EJ, Frost JA, Ward LR and Rowe B. (1996). Increasing spectrum of resistance in multiresistant *Salmonella typhimurium*. *The Lancet*, 347, 1053-4.

Threlfall EJ, Ward LR and Rowe B. (1997). Increasing incidence of resistance to trimethoprim and ciprofloxacin in epidemic *Salmonella typhimurium* DT104 in England and Wales. *Euro surveillance*. 2, 81-83. France.

Viaene J. 1997. The Swedish animal production system—Could it be applied across the European Union? University of Gent.

VMD Framework Document 1995. *MAFF PB2041*.

VPC 1996. Veterinary Products Committee Annual Report 1996, Section 4, Appendix II.

Waldergrave W. (1995) Ministerial Forward to VMD Framework Document. *MAFF PB 2041*.

Wall PG, Morgan D, Lamden K, Griffin M, Trelfall EJ, Ward LR and Rowe B. 1995. Transmission of multi-resistant strains of *Salmonella typhimurium* from cattle to man. *Vet. Rec.* 136: 591-592.

Wall PG. 1997. Personal communication with Dr Patrick Wall, PHLS.

Walton JR. 1981a. Advising on antimicrobials. *Vet Rec* 108: 366.

Walton JR. 1981b *Farmers Guardian* 19 June 1981, p 12.

Watanabe T. 1963. Infective Heredity of Multiple Drug Resistance in Bacteria. *Bacteriol Rev* 27: 87-115.

Wierup M. 1997. Ten years without antibiotic growth promoters—results from Sweden with special reference to production results alternative disease preventative methods and the usage of antibacterial drugs. WHO Meeting on medical impact of use of antimicrobial drugs in food animals. Berlin 13-17 October 1997.

Witte W. 1997. Impact of antibiotic use in animal feeding of bacterial pathogens in humans. *Antibiotic resistance: origins, evolution, selection and spread*. Wiley Chichester (Ciba Foundation Symposium) 207: 61-75.

LIST OF ENCLOSURES

1. Background article on antibiotic resistance, *The Living Earth (Soil Association Journal)* 187: 10-11, July 1995.
2. Soil Association Press Release: "Soil Associations Calls for New Approach to Antibiotics", 18 December 1996.
3. Soil Association submission to the Working Group on Microbial Antibiotic Resistance, January 1997.
4. *The Living Earth (Soil Association Journal)* 194, April 1997. Includes Editorial and Article setting out background information on the use of antibiotics in agriculture and the Soil Association's position.
5. Soil Association comments, submitted to the Veterinary Medicines Directorate, on proposed Medicated Feedstuffs and Zootechnical Feed Additives legislation. December 1997.

Memorandum by Dr J Soothill, University of Manchester

THE USE OF BACTERIOPHAGES IN THE TREATMENT OF INFECTIVE DISEASE, JAMES SOOTHILL MD MRCPATH, LECTURER IN MEDICAL MICROBIOLOGY, UNIVERSITY OF MANCHESTER

1. Bacteriophages (phages) are viruses which infect and kill bacteria, but not human or other eukaryotic cells. Each strain of phage will infect only a limited range of strains of bacteria, usually within a single species. Following the discovery of phages by Twort (1915) there were many unsubstantiated claims for their use in the treatment of bacterial infections and even of other diseases, but controlled studies failed to substantiate the claims. For example Boyd and Portnoy 1944 treated dysentery in German prisoners of war with a German commercial phage preparation and detected no benefit, but the phages had not been fully appraised before use. With the discovery of the sulphonamides and antibiotics investigation into the use of bacteriophages were largely abandoned in the west but their unassessed use in therapy in the former Soviet Union and in eastern Europe continued. Animal studies in the 1920s and 1930s gave mostly negative results eg Colvin (1932), but

Asheshov *et al* (1937) demonstrated protection of mice against typhoid. Dubos *et al* (1943) showed considerable protection against infections by *Shigella sp* of the brains of mice, phage injected into the peritoneal cavity penetrating and multiplying in the brain. Using selected well assessed phages Smith and Huggins (1981) demonstrated very great multiplication of phages in mice, whose *E coli* infections were treated more effectively than with most of the antibiotics used. They then showed great efficacy for *E coli* diarrhoea in calves, piglets and lambs (Smith and Huggins 1983, Smith *et al* 1987) and demonstrated multiplication of phage in the gut and transmission of phage from one animal to another, which is potentially of great practical value in preventing and treating infections in a herd. Berchieri *et al* (1991) protected chickens infected by *Salmonella typhimurium* but large doses of phage were needed. Since the effects of phage therapy, involving the interactions between three different groups of organisms, are inevitably complex and at present poorly understood, variable reports of effect are not surprising. Bacteriophages have one major advantage over antibiotics: they are replicated by the bacteria that are killed by them. This enables a single, small dose (Smith and Huggins 1982 Soothill 1992) to treat an infection and phage to multiply at the site of an infection, more phage being present where it is needed and less where it is not.

2. If phage therapy were to be used in humans outside the former Soviet Union and eastern Europe it would present ethical problems at first, but these might be less if the phages were used topically. *Pseudomonas aeruginosa* (*P aeruginosa*), besides causing systemic infection in immunocompromised patients, causes destruction of skin grafts in burned patients. Phage was effective in treating *P aeruginosa* and other Gram negative infections of mice (Soothill 1992) and in preventing the destruction by *P aeruginosa* of skin grafts in guinea pigs (Soothill 1994). The work supports other views that phage could be used to prevent the destruction of skin grafts in patients with burns infected with *P aeruginosa*. There is as yet no controlled evidence of effectiveness of phage treatment of infections of humans by bacteria resistant to antibiotics. Most important at present are *Staphylococcus aureus* and *Mycobacterium tuberculosis*, and there are phages effective against them *in vitro*. *In vitro* work is needed. Work in experimental animals supports the view that the treatment of antibiotic-resistant *P aeruginosa* infections of humans might be effective. Human strains of *P aeruginosa* resistant to all systemically-used antibiotics now occur and these could become an important problem, particularly with the increasing numbers of immunocompromised patients, for whom phage might be particularly suitable since clearance of phage by the patient would be reduced. Phages may also have a role in discouraging the development of antibiotic resistant organisms if they were used, when possible, for humans and perhaps more importantly, for infections of farm animals. Quinolone resistant *Salmonella sp* has been passed from farm animals to man by the eating of meat, and other resistant bacteria may also be being acquired by man from farm animals that have received antibiotics as growth promoters and for therapeutic purposes.

3. Bacteriophages are a possible alternative to antibiotics in treating antibiotic-resistant bacterial infections, with the great advantages of single dose treatment, and no established toxicity in spite of studies investigating for this. They have been used in humans in therapy in the former Soviet Union and eastern Europe and, in the USA have been given intravenously as an immunity function test (Ochs *et al*, 1971) without reported toxicity. It is possible that an allergic reaction might occur to them, but this has not been reported with purified phage. Confirmation and extension of existing tissue culture and animal toxicity studies Soothill (1992, 1993) genetic analysis for similarities with known toxin and antibiotic resistance determinants, and then appropriate controlled clinical trials are needed. Usually derived from sewage, the phages used would have had many subcultures on host bacteria and physical separations would be undertaken to remove the residue of the bacterial culture.

4. Possible limitations of bacteriophages include:

1. Narrow specificity. This can be countered by using mixtures of phages with different specificities, but phages are more likely to be useful for infections in which a specific pathogen has been isolated. The specificity has the advantage that their use does not eliminate or lead to widespread resistance in the normal flora.
2. Elimination of the phage by the immune response. This would take several days the first time a phage was used, and would be more likely to be a problem if subsequent treatments were given.
3. Poor penetration of the phage to intra-cellular organisms (e.g. mycobacterium tuberculosis) and through tissue barriers, though there is evidence of phage administered peripherally entering the brains of mice (Dubos 1943, Smith and Huggins 1982) and passing through dead skin (Soothill *et al* 1988).
4. Potentially the most important concern is that phages will introduce genes coding for virulence and for antibiotic resistance into bacteria. This could be avoided by not using phages that were lysogenic (able to incorporate their genes in a bacterium without killing it) and those with similar sequences to known virulence and antibiotic resistance determinants.

5. The above problems and concerns could potentially be overcome. More investigations into them and into the mechanisms of phage killing of bacteria are needed because of the possibility of genetic modification of the bactericidal properties of phages, and possibly the use of lysins derived from them as drugs. Although much basic research is required for the development of phage therapy recent advances in genetics will facilitate the work and the increasingly urgent need for new antibacterial agents will provide an incentive.

6. For a more detailed review of phage therapy see Barrow and Soothill (1997).

- Asheshov I, Wilson J and Topley W. 1937. *Lancet*; 319-320.
- Barrow PA and Soothill JS. 1997. *Trends in Microbiology*; 5: 268-271.
- Berchieri A, Lovell MA, and Barrow PA 1991. *Research in Microbiology*; 142: 541-549.
- Boyd JSK, and Portnoy B. 1944. *Transactions of the Royal Society of Tropical Medicine and Hygiene*; 37: 243-262.
- Colvin MG, 1932. *Journal of Infectious Disease*; 51: 17-29.
- Dubos RJ, Straus JH, and Pierce C, 1943. *Journal of Experimental Medicine*; 78: 161-168.
- Ochs HD, Starkey DD, and Wedgewood RJ. 1971. *The Journal of Clinical Investigation*; 50: 2559-2568.
- Smith HW and Huggins MB, 1982. *Journal of General Microbiology*; 128: 307-318.
- Smith HW, Huggins MB, 1983. *Journal of General Microbiology*; 129: 2659-2675.
- Smith HW, Huggins MB, and Shaw Kathleen M 1987. *Journal of General Microbiology*; 133: 1111-1126.
- Soothill JS, Lawrence JC, and Ayliffe GAJ. 1988. *Medical Science Research*; 16: 1287-1288.
- Soothill JS, 1992. *Journal of Medical Microbiology*; 37: 258-261.
- Soothill JS, 1993. MD thesis. University of London.
- Soothill JS, 1994. *Burns*; 20: 209-211.
- Twort FW, 1915, *Lancet*: 1241-1243.

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SURVEILLANCE OF THE CURRENT RESISTANCE OF NOSOCOMIAL PATHOGENS TO ANTIBACTERIALS

SUMMARY

1. The emergence of bacterial resistance to antibacterial agents continues to be an important clinical problem, although it is not shared equally by all bacterial species and classes of antibacterial agent. Gram-negative bacteria exhibit numerous drug resistance mechanisms, such as plasmid or chromosomally-mediated β -lactamases, outer membrane permeability changes that confer resistance to β -lactams and other drugs and enzymes capable of modifying non β -lactam drugs, such as the aminoglycosides. This has led to increased resistance among Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae* as well as *Enterobacter* sp. and among glucose non-fermentative Gram-negative bacilli, such as *Pseudomonas* spp., *Acinetobacter* spp., *Burkholderia* spp. and *Stenotrophomonas maltophilia*. Recent years have seen Gram-positive bacteria re-emerging as important nosocomial pathogens. Current resistance problems among Gram-positive species include methicillin resistance in staphylococci, penicillin resistance in pneumococci and vancomycin resistance in enterococci. Some organisms have acquired multiple drug resistance mechanisms making them virtually untreatable with contemporary antibacterial agents. Determination of current resistance patterns and the most appropriate empirical antibacterial treatment is best achieved by bacterial surveillance. This can be done in individual hospitals, nationally between hospitals and internationally between countries. Microbiological surveillance provides vital information on the pathogens isolated from patients, particular hospital environments and other sources, together with common patterns of antibacterial susceptibility. Surveillance is likely to be of greatest benefit in environment such as intensive care units (ICUs), where patients are at a particular risk of acquiring nosocomial infection. Other benefits include the early detection of antibacterial resistance in specific bacteria and a reduction in the inappropriate use of antibacterial agents. Studies have shown that infection control measures together with microbiological surveillance can significantly reduce infection rates and hospital costs. However, currently the collection of bacterial susceptibility data is incomplete and comprehensive national and international data are not yet established or the information is not made widely available.

INTRODUCTION

2. Since the introduction of the first antibacterial agent, the emergence of resistance has been a recognised problem. Moreover, the selection of drug-resistant organisms in serious nosocomial infections has generally been related to the widespread use of antibacterial agents [1,2]. At the time of introduction of penicillin G in 1941, less than one per cent of hospital strains of *Staphylococcus aureus* were resistant. By 1946, resistance had risen to 14 per cent and a year later to 38 per cent [3]. In the 1950s, penicillin-resistant *S. aureus* was reported widely, and following the introduction of β -lactamase stable penicillins, methicillin-resistant staphylococci were reported as early as 1961 [4]. Resistant Gram-negative bacilli emerged in the 1970s, particularly in intensive care units (ICUs) and, since the mid 1980s, strains resistant to the third-generation cephalosporins by the stable overproduction of chromosomally-mediated β -lactamases (depressed mutant) have become more widespread. *Klebsiella pneumoniae* and *Escherichia coli* producing plasmid-mediated

extended-spectrum β -lactamases (ESBLs), were first described in Germany in 1983 [5] and now occur in many hospitals world-wide [6], particularly in ICUs [7]. Recent years have seen the re-emergence of Gram-positive bacteria as the most important pathogens in community- and hospital-acquired infections [8]. Furthermore, multi-resistance among Gram-positive genera is increasing globally, particularly in pathogens such as penicillin-resistant pneumococci [9], methicillin-resistant *S.aureus* (MRSA) [8] and ampicillin-resistant enterococci that are now resistant to glycopeptides [8,9,10,11].

3. Aminoglycoside resistance has evolved by several mechanisms: reduced ribosomal binding, reduced uptake and the production of various modifying enzymes capable of phosphorylating, adenylating or acetylating these agents (APH, ANT, AAC). However, permeability mutants limiting drug access to intracellular target sites, particularly among *Pseudomonas aeruginosa*, are becoming prevalent mechanisms of aminoglycoside resistance [12,13]. Surveillance studies in some countries have demonstrated modest increases in aminoglycoside resistance among *P.aeruginosa*, *Enterobacter* spp. or *Citrobacter* spp. over time, despite acceptable infection control practices [12].

4. The new fluoroquinolones have been in clinical use for nearly 10 years. However, resistance has developed and is increasing, particularly among *P.aeruginosa* and staphylococci but has also been reported in *E.coli*, *K.pneumoniae*, *Serratia* spp. and *Acinetobacter* spp. Two mechanisms of resistance have been described; mutation of the subunit of the enzyme DNA gyrase or alteration of the porins [13]. Efflux is also an important mechanism of resistance for *S.aureus* [14].

5. The glycopeptides are large, complex antibacterials of which only two are in current use, vancomycin, introduced in the late 1950s and teicoplanin introduced in the late 1980s. Their use has increased recently as bacteria develop resistance to other antibacterial agents and with the resurgence of Gram-positive pathogens. Resistance to both has occurred among enterococci and coagulase-negative staphylococci [8,9].

6. The widespread and sometimes indiscriminate or suboptimal use of antibacterial agents has led to the development of multiple drug-resistance mechanisms, such as isoniazid and rifampicin-resistant isoniazid and rifampicin-resistant *Mycobacterium tuberculosis* [16] and glycopeptide-resistant enterococci. These organisms are resistant to almost all currently used antibacterial agents making them extremely difficult to treat.

SURVEILLANCE

7. In seriously ill patients, particularly neutropenic patients and those in the ICU, antibacterial therapy is mostly empirical and must be initiated before results of microbiological cultures are available. One way of selecting the appropriate antibacterial regimen is to monitor the local prevalence and distribution of the major pathogens and their susceptibility patterns. This can be done by surveillance: locally, in individual hospitals [16–18]; nationally, on a countrywide basis [19–21]; or internationally, between countries [22, 23]. The ability to regularly survey prevalent pathogens and their resistance patterns enables hospitals to update their prescribing policy. To be effective, surveillance programmes must use information obtained both locally from within the hospital and externally, as antibacterial agent resistance patterns may vary.

8. Regional and national data can identify general antibacterial agent resistance patterns, while local hospital information quickly identifies resistance within the institution and provides a basis for infection control measures. Data on resistance prevalence are often under-analyzed and fragmentary, and need to be generated from medial microbiology laboratories with reproducible methodology [2]. International studies have the added problem that they may only include a single hospital from individual countries and this may not reflect true resistance patterns. Surveillance data that adjust for specific infections risks, such as those associated with specific sites, devices, ICUs, surgical wound infections and other at-risk populations, may provide better inter-hospital comparisons.

9. In 1978, the World Health Organisation (WHO) recommended surveillance as a tool to provide current susceptibility data in order to monitor antibacterial resistance [24]. Currently, national or global prospective surveillance systems for monitoring antibacterial resistance as well as national and international susceptibility data are unsatisfactory and should be improved [25].

10. In the United States, various formalised systems for ongoing national surveillance provide systemic information concerning infection rates and the relative importance of pathogens. The Centers for Disease Control (CDC) and prevention has a system called the National Nosocomial Infection Surveillance (NNIS) which monitors serious infections in hospitalised patients from medical centres throughout the USA [21].

11. The American Society of Microbiology (ASM) is concerned about the national and global increase in antibacterial resistance [26, 27]. It convened the Task Force on Antibiotic Resistance comprising scientists from academic, government and industrial sectors to consider the current prevalence of antibacterial resistance, major factors affecting the emergence of antibacterial resistance, major research needs and future surveillance strategies for monitoring resistance. Their recommendations were that a national surveillance system should be established immediately [26, 27].

12. In Europe, no such active surveillance system exists and there have been few studies of nosocomial infections, particularly in the ICU environment. However, a recent international study, the European Prevalence of Infection in Intensive Care (EPIIC), was undertaken to measure the incidence of infection in

ICUs of 17 countries in Western Europe isolated on a single day in 1992 [28]. EPIIC is the largest point prevalence study of infection in ICUs and involved a total of 10,038 patients. Of these patients, 45 per cent had infections, with almost half (45.9 per cent) of these originating in the ICU. The susceptibility of the isolates was determined using routine, though standardised methodology, as recommended within the individual countries.

13. In 1975, the Paul Ehrlich Society began a study to examine the development of bacterial resistance in central Europe [29]. Data was collected from multicenter studies in Germany, Austria and Switzerland using identical methods and control systems. Australia also established a national surveillance program in 1993 [30].

14. In less developed countries, surveillance of antibacterial resistance is often more problematic. Most of the conditions that encourage antibacterial resistance development, such as self-medication, over-the-counter sales, high patient: health care worker ratio, overcrowding of hospitals, poor infection control policies and scarce documentation are present in countries such as Central and South America, Africa and Asia [13, 31–33]. Ease of travel has potentiated the spread of resistant microorganisms around the world. The WHO has been active in promoting the rational use of drugs in developing countries and monitoring the emergence of resistant organisms [34]. It has implemented an international program of antibacterial resistance surveillance, called WHONET, with the participation of 121 laboratories from 41 countries around the world.

METHODOLOGICAL DIFFERENCES

15. The problems of antibacterial resistance are often difficult to assess, as susceptibility tests with their different interpretations, standardisation and breakpoints vary from country to country, making comparisons difficult. Moreover, the detection of certain types of resistance, such as the chromosomally-mediated β -lactamases and the extended spectrum β -lactamases, should rely upon precise guidelines (eg synergy between third-generation cephalosporins and clavulante) and should be performed routinely, as susceptibility patterns of various β -lactams can vary significantly.

16. Ideally, a single standardised, quantitative and reference quality method should be used to provide comparative data for various countries around the world. A number of molecular biology techniques can be applied to confirm the identification of pathogens and detect outbreaks and resistant clones among nosocomial isolates. These include restriction enzyme analysis of genomic DNA, plasmid profiling with and without restriction enzyme analysis, ribosomal RNA probing of restricted genomic DNA, DNA sequencing of the target pathogens, pulsed field gel electrophoresis and the polymerase chain reaction (PCR). These techniques become an essential component in detecting multiple resistant organisms, as part of the infection control [35].

17. In addition, interpretation of resistance data should take into account some crucial epidemiological aspects of the studies, such as whether repeat isolates are excluded or not [36], the type of ward, the type of patients included, whether the infection is nosocomial or community-acquired [37] and the time of acquisition of the infection [38].

EPIDEMIOLOGY OF RESISTANCE

18. Over recent years, changes in the distribution of organisms and drug resistance patterns have emerged among nosocomial pathogens [39]. The five most commonly reported nosocomial pathogens in the NNIS study (1989–92) were coagulase-negative staphylococci (CNS), *E.coli*, *S.aureus*, enterococci and *P.aeruginosa* [21]. In the ICU, infections are typically caused by pathogens that are different to those found in general hospital wards and are often more refractory to antibacterial treatment [40]. The most predominant pathogens include *P.aeruginosa*, *S.aureus*, CNS, *Candida* spp., *Enterobacter* spp., enterococci, *E.coli*, *Acinetobacter* spp., *Klebsiella* spp., and streptococci [21, 28, 41]. A study conducted in 1990 between four European countries and the USA, found the most prevalent species isolated in the ICU to be: *P.aeruginosa*, *E.coli*, *Klebsiella* spp., *Acinetobacter* spp., *P.mirabilis*, *Enterobacter* sp. and *Serratia* spp [38]. The epidemiology of severe infections in the ICU is covered in detail by Wolff *et al* [41]. One of the most alarming changes over the last 10–15 years has been the gradual increase of resistant pathogens causing serious nosocomial infections. However, McGowan *et al* found that the prevalence of resistance among hospital pathogens is largely due to differences between the distribution of organisms responsible for nosocomial infections, compared to those responsible for community-acquired cases. In contrast, hospital isolates of a given organism were more resistant than the community-acquired isolates of the same organism for only some organism and drug combinations [37].

19. Several multi-resistant Gram-negative organisms are being encountered with increasing frequency in hospitals and are likely to establish themselves as serious causes of infection [42, 43]. Concern has been expressed over the increased frequency of *Acinetobacter* infections in hospitalised patients particularly in cases of nosocomial pneumoniae [38]. In a study conducted in 39 French ICUs in 1991, *Acinetobacter* spp. was the third most prevalent Gram-negative pathogen, accounting for approximately 10 per cent of all aerobic Gram-negative isolates [38]. Recently *S.maltophilia* has become a significant pathogen [44]. In the French

study, *S. maltophilia* accounted for 1.9 per cent of Gram-negative isolates in the ICU [38]. Furthermore, over the last decade *Burkholderia cepacia* has become a major threat to patients with cystic fibrosis [44]. To complicate the problem, antibacterial resistance, long considered the domain of Gram-negative bacteria, is being increasingly exhibited by Gram-positive strains [8].

20. The major mechanisms of resistance among Gram-positive and Gram-negative bacteria to β -lactams, aminoglycosides and fluoroquinolones are listed in Tables 1–3 [45].

21. The incidence of resistance among nosocomial pathogens to parenteral antibacterial agents has been studied in a surveillance study conducted in the US in 1994 [46]. Gram-positive and Gram-negative organisms isolated from 43 medical centres, using National Committee for Clinical Laboratory Standards (NCCLS) methodology, were collected (Table 4). Another large surveillance study conducted in the US examined resistance rates among 33,869 Gram-negative bacilli collected from 396 ICUs between 1990–93 [47]. The main trends in antibacterial resistance are discussed in detail below.

Staphylococci

22. *S. aureus* is causing continual concern in hospital infections due to the emergence of increasingly resistant strains, with high epidemic potential and virulence. Today, more than 90 per cent of strains of *S. aureus* have been reported as resistant to penicillin by β -lactamase production [8]. These resistant strains are usually susceptible to oxacillin, the isoxazolyl penicillins, methicillin, most cephalosporins and β -lactam/ β -lactamase inhibitor combinations.

23. Oxacillin (methicillin)-resistant strains with an additional, altered penicillin-binding protein (PBP) (PBP-2A) are increasing in frequency, and are resistant to all β -lactam compounds [8, 48]. Today MRSA is a major nosocomial pathogen found throughout the world, and associated with an increasing number of hospital infections [48–50].

24. In the USA, the percentage of MRSA among all *S. aureus* isolates from NNIS hospitals increased from 2.4 per cent in 1986 to 29 per cent in 1991 [21]. An even greater problem exists in Japan where MRSA isolates accounted for 60 per cent of all *S. aureus* strains [51]. In the EPIIC study, 60 per cent of isolates were methicillin-resistant, with the highest incidence occurring in Italy and France, although some European hospitals reported no cases caused by MRSA [28]. In another Pan-European study published in 1994, 43 laboratories from 10 countries screened a total of 7,333 consecutive isolates for methicillin-resistance. Overall the proportion of MRSA was 12.8 per cent with a range of < 1 per cent in Scandinavia to > 30 per cent in Spain, France and Italy [52].

25. Although initially susceptible to the fluoroquinolones, many strains of staphylococci now show high levels of resistance. Indeed, the overall rate of resistance to ciprofloxacin among *S. aureus* isolated in the NNIS study (1989–92) was 27 per cent, although resistance among MRSA to ciprofloxacin was as high as 80 per cent [53]. In a large study involving 78 laboratories from 12 European countries, the overall rate of resistance to ciprofloxacin among staphylococci was higher among oxacillin-resistant *S. aureus* (70.6 per cent) and oxacillin-resistant CNS (51.2 per cent) compared to oxacillin-sensitive *S. aureus* (6.5 per cent) and oxacillin-sensitive CNS (15.9 per cent) [54]. Although there is no serious evidence of vancomycin resistance in *S. aureus*, strains with reduced susceptibility to teicoplanin have been reported in France [55]. In a more recent survey, (the European collaborative study), 70 laboratories from nine countries examined the susceptibility of Gram-positive cocci to the glycopeptides, using NCCLS criteria. Out of a total of 2,852 strains, no *S. aureus* isolates were resistant to either teicoplanin or vancomycin [56].

26. Among CNS in the EPIIC study, 70 per cent were resistant to methicillin and 66 per cent resistant to gentamicin. Pooled data (1990–92) from the NNIS indicated that > 50 per cent of CNS were methicillin-resistant in the USA [21]. A high incidence of MRSA and methicillin-resistant CNS has also been reported in hospitals in Australia, Africa, South East Asia, China and South America [30, 49, 40].

27. Resistance to glycopeptides, is somewhat more common among CNS, especially *S. haemolyticus*. Such strains have been reported from France, Germany, Spain, UK and USA [56]. In the European Collaborative Study, out of a total of 1,444 CNS 0.6 per cent were resistant to teicoplanin and 0.1 per cent were resistant to vancomycin [50]. Other studies have reported teicoplanin resistance (MIC \geq 32mg/L) in 1.7–3.2 per cent of all CNS species [75].

Enterococci

28. Enterococci are a major cause of hospital-acquired infections and are a common cause of nosocomial morbidity and mortality, although there is some controversy regarding their virulence. They possess low affinity PBPs and are generally regarded as resistant to cephalosporins [8], and demonstrate a remarkable ability to acquire new resistance determinants [58]. Several problems have made the treatment of infections caused by *Enterococcus* spp difficult: β -lactamase production (rare < 1 per cent); chromosomally-mediated alterations in PBPs (frequent and > 20 per cent overall); and plasmid-mediated aminoglycoside inactivating enzyme production (up to 50 per cent), which confers high level resistance. High level resistance to streptomycin in *Enterococcus* spp is due to the production of ANT-6, whereas high-level resistance to the other aminoglycosides, including gentamicin, is due to the dual production of AAC (6') plus APH (2') or APH

(3'). Among nearly 2,000 enterococci isolated from 97 centers in the USA in 1992, 27 per cent and 36 per cent showed high level resistance to gentamicin and streptomycin, respectively.

29. More recently, resistance to vancomycin has evolved and is mediated by an altered D-alanyl-D-alanine pentapeptide terminus [59], making infections with vancomycin-resistant strains essentially untreatable. Vancomycin resistance is more common in *E. faecium* than *E. faecalis*. There are four resistance phenotypes, Van A-D, although VanA and VanB are the most prevalent. Those of the VanA phenotype are also resistant to teicoplanin, but VanB and VanC strains remain teicoplanin-susceptible, *in-vitro*.

30. Strains of glycopeptide-resistant enterococci have been found in many parts of the world, including Belgium, France, Germany, Italy, Netherlands, Spain, UK and USA [56–59]. There is evidence that the number of hospitals affected by such resistant organisms has increased in recent years, as reported from the UK [59] and the USA [58]. Out of a total of nearly 2,000 enterococci isolated from 97 centers in the USA in 1992, 23 per cent of centers reported vancomycin-resistant strains, accounting for 4.4 per cent of the total number of isolates. In 1994, this had risen to 61 per cent of centers [58]. Teicoplanin remained active *in vitro* against 28 per cent of vancomycin-resistant enterococci (VanB phenotype). An increase in glycopeptide-resistant enterococci was noted particularly in ICUs, in which the proportion of resistant isolates increased from 0.4 per cent in 1989 to 13.6 per cent in 1993. In the European Collaborative Study, 1.7 per cent of strains overall were resistant to teicoplanin and 2.3 per cent were resistant to vancomycin [56].

31. Some of the older drugs, chloramphenicol, novobiocin and doxycycline, remain active against many multiresistant enterococci although there is no generally accepted approach to the therapy of enterococcal infection due to strains resistant to penicillins, aminoglycosides and glycopeptides [57].

Pneumococci

32. Penicillin resistance in pneumococci has risen dramatically over the last 25 years and is now a global problem. Resistance is mediated by alterations in PBPs [60]. In addition to high levels of resistance to β -lactams, many strains exhibit multiple resistance to trimethoprim, sulfamethoxazole, macrolides, tetracyclines and chloramphenicol [60, 61].

33. Penicillin resistance rates (intermediate and resistant) of between 25–70 per cent have been recorded in many countries including Spain, Hungary, Israel, Chile, New Guinea, France and South Africa [60]. The incidence of penicillin-resistance strains in the UK and Australia is relatively low in comparison [61, 62]. A recent surveillance study conducted by Public Health Laboratories in the UK (PHLS) monitored penicillin resistance amongst pneumococci, and noted an increase from 0.3 per cent in 1989 to 2.5 per cent in 1994 [62]. In the USA, the CDC reported only a 5 per cent resistance rate between 1979–87 [39], with an increase to 18 per cent in 1994, with a range of 1–30 per cent [52]. In 1995, the rate was found to be 27.2 per cent in a 24-medical-center study and 23.6 per cent in a 30-center study, both conducted in 1995 [63, 64].

Escherichia coli/Klebsiella species

34. The novel extended-spectrum β -lactamases (ESBLs; mostly derivatives of TEM-1, TEM-2 and SHV-1) are of concern. They are increasing among *Klebsiella* spp and other Enterobacteriaceae such as *E. coli*, particularly in teaching hospitals and ICUs [65, 66]. Many of these strains are multi-resistant to many β -lactams and some non β -lactam antibacterials.

35. NNIS data for the USA in 1987–1991 indicated that the percentage of ceftazidime-resistant *Klebsiella* spp. increased from 1.5 per cent to 3.6 per cent, and in one hospital the incidence was as high as 39 per cent [67]. In another study conducted among 36 ICUs in the USA [47], the incidence of ceftazidime resistance among *K. pneumoniae* rose from 3.6 per cent in 1990 to 14.4 per cent in 1993 ($p \leq 0.01$). Resistance rates among *Klebsiella* isolates to ceftazidime from ICU patients have been reported to be 16 per cent in France, 11 per cent in the UK, 20 per cent in Latin America and as high as 50 per cent in Bangkok [13, 65].

36. In another European study conducted in 1990, resistance to ceftazidime among *K. pneumoniae* was 36 per cent in France, 13 per cent in Belgium and 12 per cent in the Netherlands [30]. In a further study conducted in ICUs in Western and Southern Europe, the incidence of ESBL among *Klebsiella* spp. was up to 49 per cent in Portugal and 59 per cent in Turkey [7]. Furthermore, the vast majority of ESBL isolates also have associated resistance to gentamicin and other aminoglycosides [13]. In two of these studies associated resistance to ciprofloxacin was common in certain hospitals in France [7, 38]. Fluoroquinolone resistance among *E. coli* (28 per cent) and *Klebsiella* spp. (8 per cent) has also been reported among patients with bacteraemia and cancer. This has been attributed to the widespread prophylactic use of these agents in this population, and to multiclonal emergence of resistant mutants [68, 69].

Other Enterobacteriaceae

37. Overproduction of chromosomally-mediated Bush Group 1 cephalosporins from Enterobacteriaceae confers resistance to almost all β -lactams (including third generation cephalosporins and β -lactam/ β -lactamase-inhibitor combinations) except the carbapenems. Most strains are still susceptible to the fourth-generation cephalosporins (cefpirome and cefepime). This resistance is conferred by the AmpC gene and is

characteristic of *Enterobacter*, *Citrobacter*, *Serratia* and indole-positive *Proteus* spp. Most resistance in *Enterobacter* spp. is a result of selection of pre-existing mutant organisms that produce large amounts of β -lactamase constitutively. Resistance rates against ceftazidime of up to 56 per cent have been reported and these are increasing [65,70]. Indeed, the NNIS data for 1987-1991 indicate an increase to 38.6 per cent in the USA [60]. High levels of resistance among Enterobacteriaceae (10-48 per cent) have also been observed in Europe, Latin-America and Japan [30,70]. AmpC genes have also been found on transferable plasmids in *E.coli* and *K.pneumoniae* on a worldwide scale, leading to resistance to cephalosporins, including cephamycins (eg ceftiofene) [71].

38. Ceftazidime-resistant *Enterobacter* spp. often have associated resistance to other antibacterial classes such as the aminoglycosides and the fluoroquinolones. The most prevalent aminoglycoside resistance mechanism among Enterobacteriaceae is the production of inactivating enzymes; AAC (3)-V, AAC (6')-I and APH (30-VIII) [13]. High level aminoglycoside resistance among Enterobacteriaceae may be in part plasmid-mediated and thus has the potential to be disseminated further [72]. In a surveillance study conducted in the USA between 1990 and 1993, 7 per cent of 5,451 isolates were resistant to gentamicin and tobramycin. In Latin America, aminoglycoside resistance is a more serious problem with >40 per cent of *E.cloacae* strains resistant to gentamicin and tobramycin [13]. In 1990, the overall rate of resistance to fluoroquinolones among Enterobacteriaceae in Europe was 1.8 per cent [54]. Resistance rates among Enterobacteriaceae that were above 5 per cent were *S.marcescens* (9.9 per cent), *S.liquesfaciens* (7.5 per cent), *Enterobacter aerogenes* (11.4 per cent) and *Providencia stuartii* (26.7 per cent).

Pseudomonas aeruginosa

39. Resistance among *P.aeruginosa* isolates to β -lactams can be enzyme-mediated, including both chromosomally and plasmid-mediated β -lactamases. More recently, resistance to imipenem has emerged and is attributed to both the loss of an outer membrane porin protein (predominant mechanism) and a currently rare plasmid-encoded imipenemase [73,74].

40. From the NNIS data, the incidence of ceftazidime resistance among *P.aeruginosa* isolates had not risen between 1987-1991 (10 per cent and 9 per cent), however, there was 11 per cent resistance to imipenem among > 4,000 isolates [21]. Resistance was primarily seen in isolates of patients with respiratory tract infections admitted to teaching hospitals. An increase in resistance to imipenem (0-40 per cent) in *P.aeruginosa* was also reported in specific ICUs from 1988 to 1992 [75].

41. In the EPIIC study, 46 per cent of *P.aeruginosa* isolated in the ICU were resistant to gentamicin, 28 per cent were resistant to ceftazidime and 21 per cent were resistant to imipenem, with the highest levels of resistance occurring in Greece, Italy, Spain and France. In the UK over the last eight years test results from 61 laboratories have been collected in a national computerised database, with data on 1.7 million strains. Though no attempt has been made to assess the quality of these data, each laboratory participated in external quality assurance schemes and used documented methodologies. Between 1986 and 1993, there was no change in the susceptibility pattern of *P.aeruginosa* to ceftazidime, imipenem and piperacillin (Table 5) [76].

42. Prior to their introduction in 1986, all the *P.aeruginosa* isolates were susceptible to the fluoroquinolones. Resistance has now developed, with 10 per cent of strains being resistant to ciprofloxacin by 1993. A similar level of resistance has also been recorded in other areas of the world including the USA [42,68]. In the NNIS survey, ciprofloxacin resistance among *P.aeruginosa* isolates from the respiratory tract rose from 2 per cent in 1989-1990 to 5.3 per cent in 1991-1992. In a more recent nationwide survey conducted in the USA, resistance was estimated at 18 per cent [41]. In Europe the overall rate of ciprofloxacin resistance among *P.aeruginosa* isolated from 12 countries was 13 per cent [54].

43. The incidence of aminoglycoside resistance among *P.aeruginosa* is especially high in certain Latin-American countries, where gentamicin resistance is well over 40 per cent and amikacin resistance varies from 13-24 per cent [13]. Resistance was attributed to the production of inactivating enzymes, mainly AAC(3)-V and AAC(3)-I but 30-48 per cent of isolates were resistant by impermeability.

Other non-fermentative Gram-negative bacilli

44. Numerous reports have documented the high rates of antibacterial resistance found in *Acinetobacter* spp. A particular concern has been the frequency of multiple resistance exhibited by nosocomial *Acinetobacter* spp. and the resulting therapeutic problems involved in treating patients with nosocomial infections in the ICU [77]. Most strains are resistant to aminoglycosides but some remain susceptible to third- and fourth-generation cephalosporins, imipenem and fluoroquinolones.

45. Cephalosporins resistance is mainly associated with chromosomally-mediated cephalosporinases, often in conjunction with permeability reduction and altered PBPs [77]. A potentially worrying development is the occurrence of a novel β -lactamase (ARI-1), in an imipenem-resistant strain of *A.baumannii*. This enzyme hydrolyzes imipenem and azlocillin but not the cephalosporins. Moreover, there are recent reports of hospital outbreaks which have documented the spread of imipenem-resistant strains [78].

46. *S.maltophilia* is commonly resistant to many antibacterial agents including most antipseudomonal β -lactams and aminoglycosides. Therefore treatment of infections caused by this pathogen can be difficult

[44, 79]. The main enzymatic mechanism of resistance is the production of zinc-metallo carbapenemase which confers high levels of resistance to imipenem, meropenem and other β -lactam compounds. Mechanically ventilated patients, receiving antibacterial agents (particularly carbapenems), are at increased risk of becoming colonised or infected with this organism.

47. *B. cepacia* is resistant to a wide range of antibacterial agents including polymyxin, aminoglycosides, some fluoroquinolones and the antipseudomonal penicillins. Other β -lactams such as some third and fourth-generation cephalosporins, temocillin, imipenem, sulbactam, fosfomycin and ciprofloxacin display some activity against this organism, although there is evidence that some strains produce a carbapenemase [44, 80].

IMPLICATIONS OF SUSCEPTIBILITY CHANGES ON THERAPEUTIC CHOICE

48. When a serious nosocomial infection is suspected, treatment must be commenced immediately to increase the likelihood of a satisfactory outcome. As described previously, the choice of the most appropriate antibacterial agent for empirical treatment should be guided by the information generated from recent local surveillance. When both Gram-negative and Gram-positive organisms are implicated, a broad-spectrum antibiotic or combination of more narrow-spectrum antibiotics can be selected as the choice of empirical therapy.

49. Emerging resistance problems limit the utility of currently available antibacterial agents [27]. Problems with resistance to penicillins led to cephalosporins becoming the preferred β -lactams. Although the third-generation cephalosporins have broad-spectrum activity they have deficiencies in their antibacterial spectrum. Ceftazidime has the greatest spectrum of activity among the third-generation cephalosporins against Gram-negative organisms and is used frequently in the treatment of serious infections. However, it lacks consistent activity against Gram-positive pathogens, most importantly staphylococci. The new fourth-generation cephalosporins (ie ceftiprome and cefepime) and the carbapenems (imipenem and meropenem) both have broad-spectrum activity which includes most Gram-negative and Gram-positive organisms that cause serious infections in the ICU, including most Enterobacteriaceae, *P. aeruginosa* and methicillin susceptible staphylococci.

50. A number of surveillance studies conducted in the USA and Europe have examined current susceptibility patterns of nosocomial isolates to a range of broad-spectrum antibacterial agents. One large study examined the susceptibility of a total of 41,000 clinical isolates to 22 antibacterial agents (at least 5,000 isolates per compound) isolated in 236 medical centers, using standardised disk diffusion tests [81]. The drugs were ranked in order of activity against the total number of pathogens (Table 6). Overall, piperacillin-tazobactam and imipenem were the most often active, inhibiting > 90 per cent of isolates, followed by ofloxacin (87 per cent), ciprofloxacin (82 per cent) and ceftazidime (75.5 per cent). Another study re-evaluated a further 5,000 strains, after 5 years, isolated from five medical centers and included the fourth-generation cephalosporin cefepime [82]. Imipenem and piperacillin-tazobactam had < 90 per cent inhibition of all isolates followed by the fourth-generation cephalosporin (> 85 per cent). All the other drugs had \leq 79.4 per cent inhibition (Table 6). The overall susceptibility to some fluoroquinolones was lower in this study than one previously reported by Murray *et al* [83] (91 per cent). In a further study of 8,500 Gram-positive and Gram-negative hospital isolates conducted in the USA, 83.4 per cent were susceptible to ofloxacin and 82 per cent to ciprofloxacin, respectively [46].

51. In a European study conducted in 1990 [84], the epidemiology and susceptibility of 8,625 ICU and hematology bacterial isolates were determined to third and fourth-generation cephalosporins and imipenem using NCCLS methodology. Cefpirome and imipenem exhibited the least resistance, followed by cefotaxime, ceftazidime and ceftriaxone. The study showed that > 83 per cent of all isolates were susceptible to imipenem and cefpirome and 70 per cent were susceptible to ceftazidime. Cefpirome and imipenem were also the most active agents against organisms resistant to ceftazidime (Table 7) [85]. These results are in agreement with a US study, where the activity of cefpirome was compared with all clinically available third-generation cephalosporins against nearly 6,000 recent clinical isolates from five medical centers, using standardised NCCLS methodology [86].

52. All these studies indicate that the new fourth-generation cephalosporins, the carbapenems and piperacillin-tazobactam have broad-spectrum activity and are likely to encounter few resistant strains at present. However as these agents are increasingly used, resistance will undoubtedly follow.

STRATEGIES TO REDUCE DEVELOPMENT

53. The use of antibacterial agents can exert a selective pressure that favours the emergence of drug-resistant organisms which then accumulate in the hospital environment. Improved infection control policies should minimise this problem. The ASM has recommended that a number of issues should be addressed such as reducing the overprescribing of antibacterials and resulting resistance selective pressures, reducing or modifying the public expectations of the need for antibacterials for nonbacterial infections and reducing the use of antibacterials in animal food production [26, 27].

54. Studies should be initiated to define more accurately the risks of drug-use patterns on the selection of resistant microbial strains. When usage is associated with emerging resistance, interventions at local, regional

or national levels should be initiated to limit the problem. Furthermore, institutions must practise proper infection control to prevent the horizontal transfer of drug-resistant organisms (mutants or plasmid-mediated). Standards of infection control in hospitals are needed, as is the use of standardised methods that have been validated, quality controlled and quality assured [30]. Close adherence to infection control policies should reduce the spread of infections and (multi)-resistant strains. There is strong evidence that strict adherence to infection control procedures can prevent nosocomial outbreaks with these organisms.

55. It may be possible by switching or cycling antibiotics to minimise the selection of drug-resistant organisms. A cycling scheme for the aminoglycosides has been established [87] and should be evaluated for the β -lactams. The widespread use of third-generation cephalosporins has led to the emergence of resistant Enterobacteriaceae caused by various β -lactamase-resistance mechanisms [27]. Indeed, when ceftazidime was used in excess in the hospital environment, a resistant subpopulation of cephalosporins stably overproducing mutants was selected [67]. Complete removal or diminished use of this compound has resulted in a decline in resistant rates [88].

56. In 1996 Sanders *et al* proposed a cycling scheme for the empirical therapy of Gram-negative infections, whereby every two months three β -lactams plus or minus an aminoglycoside were cycled [89]. The β -lactams suggested were a penicillin plus or minus a β -lactamase inhibitor, a fourth-generation cephalosporin (cefpirome or cefepime) and a carbapenem. The precise drugs used for each cycle should be tailored to fit the needs of the unit. For example, if *P.aeruginosa* is a problem pathogen for the unit, an antipseudomonal penicillin will be preferred for the penicillin phase of the cycle while ampicillin may be preferred for units with problems with Gram-positive organisms.

57. It is important to note the cycling scheme is for empirical therapy only. Once the etiological agent of infection has been identified, the patient must be switched to another therapy specifically targeted for the pathogen isolated.

58. A scheme to cycle antibiotics can consist of any number of antibiotics, however the effectiveness of the cycle depends upon how diligently it is adhered to and the appropriateness of the antibacterials chosen for the specific site in question.

59. As it is very difficult or impossible to predict the bacterial resistance that will be evolving, microbiological surveillance studies will continue to be necessary to detect future trends in antibacterial resistance. In many cases, the mechanisms of resistance (ie susceptibility or resistance to several drugs taken together) rather than resistance to each drug taken separately.

CONCLUSION

60. Continued surveillance of antibacterial susceptibility patterns is an integral part of monitoring the development of resistance. Since resistance develops over a period of time, surveillance must be maintained to detect trends [89]. When used appropriately by physicians, health administrators and the commercial pharmaceutical industry, surveillance data can offer economic as well as health benefits to health care systems [90].

61. Within each hospital, continual surveillance of prevalent strains and their resistance patterns is fundamental as a means of establishing the significance of resistance in clinical infection and in determination of hospital prescribing policies [91]. There is also a need for national data to assist the formulation of policies for the supply and use of antibacterial agents in man and animals and to encourage responsible action by manufacturers in the promotion of their products [34]. As newer agents take the place of older ones, rational prescribing of existing drugs is needed. This may be obtained through education and with the application of national and supranational networks of surveillance, which will anticipate trends in resistance.

Table 1

RESISTANCE FOR MECHANISMS FOR β -LACTAM ANTIBIOTICS (PENICILLINS, CEPHALOSPORINS, MONOBACTAMS, CARBAPENEMS) USED TO TREAT SEVERE INFECTIONS, DATA ADAPTED FROM NEU [45]

Antimicrobials	Mechanisms	Genetic Basis	Crisis Now	Future Crisis
β -lactams	Altered penicillin binding proteins	Chromosomal	<i>S.pneumoniae</i> <i>S.epidermidis</i> <i>S.aureus</i>	<i>N.meningitidis</i>
	Reduced permeability	Chromosomal	<i>P.aeruginosa</i> <i>E.cloacae</i> <i>S.marcescens</i> <i>K.pneumoniae</i>	
	β -lactamase	Plasmid or Chromosomal	<i>Stenotrophomonas</i> <i>Acinetobacter</i> spp Enterobacteriaceae	<i>Bacteroides</i> spp <i>N. meningitidis</i> Enterococci

Table 2

RESISTANCE MECHANISMS FOR FLUOROQUINOLONES (NORFLOXACIN, OFLOXACIN, CIPROFLOXACIN, LOMEFLOXACIN) USED TO TREAT SEVERE INFECTIONS, DATA ADAPTED FROM NEU [45]

Antimicrobials	Mechanisms	Genetic Basis	Crisis Now	Future Crisis
Fluoroquinolones	Altered DNA gyrase	Chromosomal	MRSA <i>Pseudomonas</i> <i>S.pneumoniae</i>	Enterobacteriaceae <i>Haemophilus</i> spp <i>N.gonorrhoeae</i>
	Reduced permeability	Chromosomal	<i>Serratia</i> spp <i>P.aeruginosa</i>	Enterobacteriaceae
	Modification of topoisomerase IV	Plasmid	<i>S.pneumoniae</i> <i>S.aureus</i>	
	Efflux	Chromosomal		<i>S.aureus</i>

Table 3

RESISTANCE MECHANISMS FOR AMINOGLYCOSIDES (GENTAMICIN, AMIKACIN, TOBRAMYCIN) USED TO TREAT SEVERE INFECTIONS, DATA ADAPTED FROM NEU [45]

Antimicrobials	Mechanisms	Genetic Basis	Crisis Now	Future Crisis
Aminoglycosides	Decreased ribosomal binding	Chromosomal	Streptococci	
	Reduced uptake	Chromosomal		Enterobacteriaceae
	Modifying enzymes	Plasmid	Enterococci <i>Pseudomonas</i> Enterobacteriaceae	Streptococci

Table 4

BASELINE ANTIMICROBIAL RESISTANCE PATTERNS REPORTED IN 43 CENTERS IN THE US FROM 1993–94, DATA SELECTED FROM JONES ET AL [46]

Resistant Organism	Percent Resistant	Average	Method adjusted rate ^a
Penicillin-resistant <i>Streptococcus pneumoniae</i>	1–30	7.9	17.8
Ampicillin-resistant enterococci			
<i>Enterococcus faecalis</i>	1–3	1.7	
<i>Enterococcus faecium</i>	20–82	56.9	

^a Rate observed when using more accurate E test System (AB Biodisk, Solna, Sweden)

Resistant Organism	Percent Resistant	Average	Method adjusted rate ^a
Group 1 cephalosporins resistance ^b			
<i>Citrobacter freundii</i>	2-60	28.4	
<i>Enterobacter cloacae</i>	5-58	31.0	
<i>Pseudomonas aeruginosa</i>	2-28	12.2	
Extended-spectrum β -lactamase ^b			
<i>Escherichia coli</i>	1-39	5.4	
<i>Klebsiella</i> spp.	1-58	7.1	
Imipenem resistance			
<i>Enterobacter</i> spp	1-9	4.0	
<i>Morganella morganii</i> ^c	9-46	20.8	
<i>Proteus mirabilis</i> ^c	3-34	17.9	0.5
<i>Pseudomonas aeruginosa</i>	4-24	11.2	9.7
<i>Serratia marcescens</i>	1-13	5.2	
<i>Stenotrophomonas maltophilia</i>	84-100	93.0	
Vancomycin resistance			
Coagulase-negative staphylococci	1-3	1.5	
Enterococci			7.9 (all species)
<i>Enterococcus faecalis</i>	0.2-22	5.2	
<i>Enterococcus faecium</i>	1-42	15.6	
Fluoroquinolone resistance ^d			
<i>Staphylococcus aureus</i>			24.9 (all strains)
oxacillin-resistant	3-100	64.3	
oxacillin-susceptible	1-84	17.1	
coagulase-negative staphylococci			
oxacillin-resistant	4-91	51.3	
oxacillin-susceptible	3-90	23.2	
<i>Citrobacter freundii</i>	1-24	8.0	9.9
<i>Enterobacter</i> spp	1-33	6.6	
<i>Escherichia coli</i>	0.2-27	2.6	0.8
<i>Klebsiella</i> spp	1-32	6.3	
<i>Serratia</i> spp	3-39	14.1	6.8
<i>Pseudomonas aeruginosa</i>	5-90	18.1	14.9
<i>Pseudomonas</i> spp	8.75	34.1	
<i>Stenotrophomonas maltophilia</i>	14-100	45.0	

Table 5

P. AERUGINOSA SUSCEPTIBILITY IN THE UK, 1986-96,
DATA SELECTED FROM
SPENCER [76]

Compound	% susceptible (number of strains tested)	
	1986	1993
Gentamicin	94 (1939)	92 (1709)
Imipenem	ND	89
Ceftazidime	97 (1308)	96 (1664)
Ciprofloxacin	100 (8)	90 (1559)
Piperacillin	93 (1458)	93 (957)

ND = No data

^a Rate observed when using more accurate E test System (AB Biodisk, Solna, Sweden)

^b Based on ceftazidime resistance rate

^c These species only moderately susceptible to imipenem

^d Based on ciprofloxacin resistance rate

Table 6

RANKED OVERALL SUSCEPTIBILITY (%) OF PARENTAL ANTIMICROBIAL AGENTS TESTED AGAINST > 5,000 AEROBIC ISOLATES (GRAM-POSITIVE AND GRAM-NEGATIVE) FROM THE US (1989-94), DATA ADAPTED FROM BARON *ET AL* AND MARSHALL *ET AL* [81,82]

<i>Antimicrobial agent</i>	<i>1989^a</i>	<i>1994^b</i>
Piperacillin-tazobactam	92	93.5
Imipenem	93.6	93.5
Cefepime	NT	86.7
Ofloxacin	87	NT
Ceftazidime	75.5	79.4
Gentamicin	77	NT
Ticarcillin-clavulante	73.3	74.5
Ceftriaxone/cefotaxime	72	74
Ampicillin/sulbactam	NT	72.6
Piperacillin	NT	61
Ticarcillin	NT	44.5
Ampicillin	NT	33.3

NT = Not tested

Table 7

ACTIVITY OF β -LACTAMS AGAINST CEFTAZIDIME-RESISTANT BACTERIA, DATA SELECTED FROM SPENCER [85]

<i>Organism</i>	<i>n</i>	<i>Cefpirome</i>	<i>% sensitive to^c Ceftriaxone</i>	<i>Imipenem</i>	<i>Piperacillin</i>
<i>E.coli</i>	42	69	17	86 ^d	29
<i>Klebsiella</i> spp	91	47	15	90 ^d	3
<i>Enterobacter</i> spp	205	73	7	94	9
<i>Citrobacter</i> spp	38	92	11	100	13
<i>Proteus</i> spp	28	54	39	79 ^e	46
<i>P.aeruginosa</i>	213	11	0	66	19

REFERENCES

1 McGowan JE. Antimicrobial resistance in hospital organisms and its relation to antimicrobial agent use. *Rev Infect Dis* 1983; 5: 1033-48.

2 O'Brien TF and The Members of the Task Force. Resistance of bacteria to antimicrobial agents: Report of task force 2. *Rev Infect Dis* 1987; 9: S244-60.

3 Towner KJ. The problems of resistance. In Greenwood D eds. *Antimicrobial Chemotherapy*. Oxford Medical 3rd Edition 1995; 139-46.

4 Barber M. Methicillin-resistant staphylococci. *J Clin Pathol* 1961; 14: 385.

5 Knothe H, Shah P, Kremery V, Anatal M, Mitsuhashi S. Transferable resistance to cefotaxime, ceftazidime, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens*. *Infection* 1983; 11: 315-7.

6 Jacoby FA, Medeiros AA. More extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 1991; 35: 1697-704.

7 Livermore DM, Yuan M. Antimicrobial agent resistance and production of extended-spectrum

^a Represents data from 5,889 strains interpreted by current NCCLS (1994) criteria

^b Represents data from 5,039 strains interpreted by current NCCLS criteria

^c Sensitivity based on NCCLS breakpoints

^d Uncontrolled results

^e This species only moderately susceptible to imipenem

- β -Lactamases amongst *Klebsiella* spp. from intensive care units in Europe. *J Antimicrob Chemother* 1996; 38: 409-24.
- 8 Howe RA, Brown NM, Spencer RC. The new threats of Gram-positive pathogens: re-emergence of things past. *J Clin Pathol* 1996; 49: 444-9.
- 9 Applebaum PC. Emerging resistance to antimicrobial agents in Gram-positive bacteria. *Drugs* 1996; 51: (Suppl 1): 1-15.
- 10 Uttley AHC, Colins CH, Naidoo J, George RC. Vancomycin-resistant enterococci. *Lancet* 1988; i: 57-8.
- 11 Lacleq R, Derlot E, Duval J, *et al.* Plasmid-mediated resistance to vancomycin in *Enterococcus faecium*. *New Engl J Med* 1988; 316: 157-61.
- 12 Young LS, Hindler J. Aminoglycoside resistance: a worldwide perspective. *Am J Med* 1986; (suppl 6b): 15-21.
- 13 Casellas JM, Blanco, MG, Pinto ME. The sleeping giant. Antimicrobial resistance. *Infect Dis Clin N Amer* 1994; 8: 29-45.
- 14 Kaatz, GW, Seo SM, Ruble A. Efflux-mediated fluoroquinolone resistance in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1993; 67: 1086-94.
- 15 Spencer RC, Wheat PF, Harris DM. Microcomputer surveillance as an aide to rational antimicrobial agent therapy for urinary tract infection (UTI) in general practice. *Health Trends* 1986; 4: 84-6.
- 16 Bloch AB, Cauthen GM, Onorato IM *et al.* Nationwide survey of drug-resistant tuberculosis in the United States. *JAMA* 1994; 271: 665-71.
- 17 Gordts B, Van Landuyt HW. Importance and realisation of a surveillance programme on local epidemiology of bacterial resistance. *Br J Clin Prac* 1988; 57: 11-4.
- 18 Stobberingh, EE, Phillips JM, Houben AW, van Boven CP. A regional survey of the resistance to β -lactam antimicrobial agents in clinical isolates of (facultative) aerobic micro-organisms. *Drugs* 1988; 35: 41-4.
- 19 Lorian V, Atkinson BA. Bacterial resistance to antimicrobial agents in the United States. Ten million strains, nine species and sixteen antimicrobial agents. *Drugs under Exp Clin Res* 1987; 13: 457-77.
- 20 Nicoletis MAL, Baccala LA. Time series analysis of rhythmic bacterial resistance development to antimicrobial agents *Comput Biomed Res* 1988; 21: 137-57.
- 21 Jarvis WR, Martone W. Predominant pathogens in hospital infections. *J Antimicrob Chemother* 1992; 29 (suppl A): 19-24.
- 22 O'Brien TF, Kent RL, Medeiros AA. Computer generated plots of a result antimicrobial susceptibility tests. *J Am Med Assoc* 1969; 210: 84-92.
- 23 O'Brien TF. Resistance to antimicrobial agents at medical centres in different parts of the world. *J Antimicrob Chemother* 1986; 18: 243-53.
- 24 WHO Surveillance for the prevention and control of health hazards due to antimicrobial agent resistant enterobacteria: report of a WHO meeting. World Health Organisation Technical Report, 1978; Series No 624: 1-54.
- 25 Lorian V. The need for surveillance for antimicrobial resistance. *Infect Control Hosp Epidemiol* 1995; 16: 638-41.
- 26 American Society for Microbiology Report of the ASM Task Force on antibiotic resistance. *Antimicrob Agents Chemother* 1995; (suppl 6): 1-23.
- 27 Jones RN. The emergence needs for basic research, education and surveillance of antimicrobial resistance. *Diagn Microbiol Infect Dis* 1996; 25: 1-9.
- 28 Vincent JL, Bihari DJ, Suter PM *et al* The prevalence of nosocomial infection in intensive care units in Europe. *JAMA* 1995; 274: 639-45.
- 29 Wiedermann B. Epidemiology, control and treatment of multiresistant Gram-negative rods. *Drugs* 1996; (suppl 2): 95-102.
- 30 Bell J, Turnidge J. National Antimicrobial Resistance Surveillance Program, 1993 Report. Melbourne, 1995.
- 31 Rossi MA, Tokumoto M, Couto E *et al.* Survey of the levels of antimicrobial resistance in Argentina: WHONET programme—1991 to 1994. *Int J Antimicrob Agents* 1995; 6: 103-10.
- 32 Kunin CM. Resistance to antimicrobial drugs—a world wide calamity. *Ann intern med* 1993; 118: 557-61.
- 33 Kunin CM, Lipton HL, Tupasi T, *et al.* Social, Behavioral and Practical Factors affecting antibiotic use worldwide: Report of Task Force 4. *Rev Infect Dis*; 9: (suppl 3) 270-85.
- 34 World Health Organisation Scientific working group on antibacterial resistance. Control of antimicrobial agent-resistant bacteria: memorandum from a WHO meeting. *Bull WHO* 1983; 61: 423-433.

- 35 Peterson LR, Petzel RA, Clabots CR, Fashing CE, Gerding DN. Medical technologies using molecular epidemiology as part of the infection control team. *Diagn Microbiol Infect Dis* 1993; 16: 303-311.
- 36 Houvinen P. Recording of antimicrobial resistance of urinary tract isolates—effect of repeat samples on resistance levels. *J Antimicrob Chemother* 1985; 16: 443-7.
- 37 McGowan JE Jr, Hall EC, Parrott PL. Antimicrobial susceptibility in Gram-negative bacteria: Are nosocomial isolates really more resistant? *Antimicrob Agents Chemother* 1989; 33: 1855-59.
- 38 Jarlier V, Fosse T, Phillippon A and the ICU Study Group. Antibiotic susceptibility in aerobic Gram-negative bacilli isolated in intensive care units in 39 French teaching hospitals (ICU study). *Intensive Care Med* 1996; 22: 1057-65.
- 39 Schaberg DR, Culver DH, Gaynes RP. Major Trends in the microbial etiology of nosocomial infection. *Am J Med* 1991; (suppl 3B): 72-5.
- 40 Pierson CL, Friedman B. Comparison of susceptibility to β -lactam antimicrobial agents among bacteria isolated from intensive care units. *Diagn Microbiol Infect Dis* 1992; 15: 19S-30S.
- 41 Wolff M, Brun-Buisson C, Lode H, Mathai D, Lewi D, Pittet D. The changing epidemiology of severe infections in the ICU. *Clin Micro Infect* 1997; 3 (suppl 1): 36-7.
- 42 Spencer RC. Nosocomial infection in the intensive care unit: a question of surveillance. *Intensive Care World* 1993; 10: 173-6.
- 43 McGowan JE Jr. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Rev Infect Dis* 1983; 5: 1033-48.
- 44 Spencer RC. The emergence of epidemic, multiple-antibiotic resistant *Stenotrophomonas* (*Xanthomonas*) *maltophilia* and *Burkholderia* (*Pseudomonas*) *cepacia*. *J Hosp Infect* 1995; 30 (suppl): 435-64.
- 45 Neu HC. The crisis in antibiotic resistance. *Science* 1992; 257: 1064-73.
- 46 Jones RN, Kehrberg EN, Erwin ME, Anderson SC and the Fluoroquinolone Resistance Surveillance Group. Prevalence of important pathogens and antimicrobial activity of parenteral drugs at numerous medical centers in the United States, I: study on the threat of emerging resistances: real or perceived? *Diagn Microbiol Infect Dis* 1994; 19: 203-15.
- 47 Itakazu GS, Quinn JP, Bell-Dixon C, Kahan FM, Weinstein RA. Antimicrobial resistance rates among aerobic Gram-negative bacilli recovered from patients in Intensive Care Units: Evaluation of a post-marketing Surveillance Program. *Clin Infect Dis* 1996; 23: 77-84.
- 48 Panlilio AL. Methicillin-resistant *Staphylococcus aureus* in US hospitals, 1975–1991. *Infect Control Hosp Epidemiol* 1992; 13: 582-6.
- 49 Voss A, Doebbeling BN. The world-wide prevalence of methicillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents* 1994; 5: 101-6.
- 50 Turnidge JD, Nimmo GR, Francis G. Evolution of resistance in *Staphylococcus aureus* in Australian teaching hospitals. *Med J Aust* 1996; 164: 68-71.
- 51 Kimura A, Igarashi H, Ushioda H, *et al*. Epidemiological study of *Staphylococcus aureus* isolates from Japanese national united and medical college hospitals. *Kansen Shogaku-Zasshi* 1992; 66: 1543-9.
- 52 Voss A, Milatovic D, Wallrauch-Schwarz C, Rosdahl VT, Braveny I. Methicillin-resistance in Europe. *Eur J Clin Microbiol Infect Dis* 1994; 13: 50-5.
- 53 Coronado V, Gaynes, Edwards J. The National Nosocomial Infection Surveillance System. Ciprofloxacin resistance among nosocomial *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the United States. *Infect Control Hosp Epidemiol* 1994; 15: 23.
- 54 Kresken M, Hafner D, Mittenmayer H, *et al* and the Study Group “Bacterial Resistance” of the Paul Ehrlich Society for Chemotherapy. Prevalence of Fluoroquinolone resistance in Europe. *Infection* 1994; 22 (suppl 2): 90-8.
- 55 Vedel G, Lervez M, Lemman F, *et al*. Prevalence of *Staphylococcus aureus* and coagulase-negative staphylococci with decreased sensitivity to glycopeptides as assessed by determination of MICs. *Eur J Clin Microbiol Infect Dis* 1990; 9: 820-2.
- 56 Verbist L, Bauenfeind A, and the European Glycopeptide Resistance Group. *Comparative susceptibility of Gram-positive clinical isolates to teicoplanin*. 1996; 10th Mediterranean Congress of Chemotherapy.
- 57 Cormican MG, Jones RN. Emerging resistance to antimicrobial agents in Gram--positive bacteria—Enterococci, staphylococci and nonpneumococcal streptococci. *Drugs* 1996; 51 (suppl 1): 612.
- 58 Jones RN, Sader HS, Erwin ME, Anderson SC. Emerging multiply resistant enterococci among clinical isolates. 1. Prevalence data from 97 medical center surveillance study in the United States. Enterococcus Study Group. *Diagn Microbiol Infect Dis* 1995; 21: 85-93.
- 59 Woodford N, Johnson AP, Morrison D, Speller DCE. Current perspectives on glycopeptide resistance. *Clin Microbiol Rev* 1995; 8: 585-615.

- 60 Klugman K, Goldstein F, Kohno S, Baquero F. The role of fourth-generation cephalosporins in the treatment of infections caused by penicillin-resistant streptococci. *Clin Micro Infect* 1997; 3 (suppl 1): 48-60.
- 61 Colligson PJ, Bell JM. Drug-resistant *Streptococcus pneumoniae*, the beginning of the end for many antibiotics? *Med J Aust* 1996; 164: 64-7.
- 62 Speller DCE, Johnson AP, Cookson BD, Waight P, George RC. PHLS surveillance of antimicrobial agent resistance, England and Wales: Emerging Resistance in *Streptococcus pneumoniae*. *Emerging Infect Dis* 1996; 2: 57.
- 63 Thornsberry C, Burton PH, Vanderhoof BH. Activity of penicillin and three third-generation cephalosporins against US isolates of *Streptococcus pneumoniae*. A 1995 surveillance study. *Diagn Microbiol Infect Dis* 1996; 25: 89-95.
- 64 Doern GV, Bruggeman A, Holley H. *pylori*, Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during Winter months of 1994 to 1995: Results of a 30 centre National Surveillance Study Antimicrob Agents Chemother 1996; 4: 1208-13.
- 65 Quinn JP. Clinical significance of extended-spectrum beta lactamases. *Eur J Clin Microbiol Infect Dis* 1994; 1: 39-42.
- 66 Phillipon A, Ben Rebjebe S, Fournier G, Ben Hassen A. Epidemiology of extended spectrum β -lactamases. *Infection* 1989, 12: 347-50.
- 67 Burwen DR, Banjeree SN, Gaynes RP, the National Nosocomial Infections Surveillance System. Ceftazidime resistance among selected nosocomial Gram-negative bacilli in the United States. *J Infect Dis* 1994; 170: 1622-5.
- 68 Cometta A, Calandra T, Billie J, Glauser MP. *Escherichia coli*-resistant to fluoroquinolones in patients with cancer and neutropenia. *N Engl J Med* 1994; 1240.
- 69 Bauernfeind A, Abele-Horn M, Emmering P, Jungwirth R. Multiclonal emergence of ciprofloxacin-resistant clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae*. *J Antimicrob Chemother* 1994; 34: 1075-6.
- 70 Sanders WE, Sanders CC. Inducible β -lactamases: clinical and epidemiological implications for use of newer cephalosporins. *Rev Infect Dis* 1988; 10: 830-8.
- 71 Bauernfeind A, Stemplinger I, Jungwirth R, Wilhelm R, Chong Y. Comparative characterisation of the cephamycinase bla CMY-1 gene and its relationship with other β -lactamase genes. *Antimicrob Agents Chemother* 1996; 1926-30.
- 72 Phillips I, King A, Shannon K. Prevalence and mechanisms of aminoglycoside resistance, *Am J Med* 1986; 80 (suppl 6B): 48-55.
- 73 Trias J, Nikaido H. Outer membrane protein D2 catalyzes facilitated diffusion of carbapenems and penems through the outer membrane of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1990; 34: 52-7.
- 74 Watanabe M, Iyobe S, Inoue M, *et al.* Transferable imipenem resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1991; 35: 147-51.
- 75 Stratton CW, Ratner H, Johnston PE, Schaffner W. Focused microbiologic surveillance by specific hospital unit as a sensitive means of defining antimicrobial resistance problems. *Diagn Microbiol Infect Dis* 1992; 15: 3S-10S.
- 76 Spencer RC. An 8 year microbe base survey of the epidemiology, frequency and antimicrobial agents susceptibility of *Pseudomonas aeruginosa* hospital isolates in the United Kingdom. *J Antimicrob Chemother* 1996; 37: 295-301.
- 77 Bergogne-Berezin E, Towner KJ. *Acinetobacter* spp. as nosocomial pathogens: Microbiological, clinical and epidemiological features. *Clin Microbiol Rev* 1996; 9: 148-65.
- 78 Tankovic J, Legrand P, De Gatines G, Chemineau V, Brun-Buisson C, Duval J. Characterisation of a hospital outbreak of imipenem-resistant *Acinetobacter baumannii* by phenotypic and genotypic methods. *J Clin Microbiol* 1994; 32: 2677-81.
- 79 Vartivarian S, Anaisse E, Bodey G, Sprigg H, Royston K. A changing pattern of susceptibility of *Xanthomonas maltophilia* to antimicrobial agents: implication for therapy. *Antimicrob Agents Chemother* 1994; 38: 624-7.
- 80 Kerr JR. *In-vitro* activity of this drug combinations of ceftazidime, cefotaxime, cefuroxime, ciprofloxacin, chloramphenicol, imipenem and temocillin against clinical isolates of *Pseudomonas cepacia* from patients with cystic fibrosis. *Int J Antimicrob Agents* 1993; 3: 205-9.
- 81 Baron EJ, Jones RN. National Survey of the *in-vitro* spectrum of piperacillin-tazobactam tested against more than 40,000 aerobic clinical isolates from 236 medical centers. *Diagn Microbiol Infect Dis* 1995; 21: 141-51.
- 82 Marshall SA, Aldridge KE, Allen SD, Fuchs PC, Gerlach EH, Jones RN. Comparative antimicrobial

- activity of piperacillin-tazobactam tested against more than 5,000 recent clinical isolates from five medical centers. A re-evaluation after five years. *Diagn Microbiol Infect Dis* 1995; 21: 153-68.
- 83 Murray PR, Cantrell HF, Lankford RB. Multicenter evaluation of the *in-vitro* activity of piperacillin/tazobactam compared with 11 selected β -lactam antimicrobials and ciprofloxacin against more than 42,000 Gram-positive and Gram-negative bacteria. *Diagn Microbiol Infect Dis* 1994; 19: 111-20.
 - 84 Verbist L. Epidemiology and sensitivity of 8,625 intensive care unit and haematology/oncology bacteria isolates in Europe. *Scand J Infect Dis* 1991; 91: 14-24.
 - 85 Spencer RC. Cross-susceptibility of ceftiofime and four other β -lactams against isolates from haematology/oncology and intensive care units. *Scand J Infect Dis* 1991; 78: S24-32.
 - 86 Jones RN, Pfaller MA, Allen SD, Gerlach EH, Fuchs PC, Aldridge KE. Antimicrobial activity of ceftiofime: an update compared to five third-generation cephalosporins against nearly 6,000 recent clinical isolates from five medical centers. *Diagn Microbiol Infect Dis* 1991; 14: 361-4.
 - 87 Jones RN. The current and future impact of antimicrobial resistance among nosocomial bacterial pathogens. *Diagn Microbiol Infect Dis* 1992; 15: S3-S10.
 - 88 McGowan JE Jr. Minimising Antimicrobial resistance in hospital bacteria: Can switching or cycling drugs help? *Infect Control* 1986; 7: 573-7.
 - 89 Sanders WE, Sanders CC. Cycling of antibiotics: an approach to circumvent resistance in specialised units of the hospital. *Clin Microbiol Infect* 1996; 1: 223-5.
 - 90 Brown EH, Spencer RC, Brown JMC. The emergence of bacterial resistance in hospitals—a need for continual surveillance. *J Hosp Infect* 1990; 15: S35-40.
 - 91 POST Report (Parliamentary Office of Science and Technology). Diseases fighting back—The growing resistance of TB and other bacterial diseases to treatment 1994.

Memorandum by Dr John Sterland

1. I work as a busy GP and write 10–20 prescriptions for antibiotics every day.
2. Most of these prescriptions are demanded and expected by my patients.
3. As most (85 per cent) patients are exempt from prescription charges there is no cost to them.
4. Misuse is therefore widespread.
5. There should be a small financial disincentive for all antibiotic use.
6. More complex and expensive agents should cost the patient more so that they will favour cheaper preparations, so limiting inappropriate exposure and therefore resistance.
7. In summary, if only patients could be involved with the cost of antibiotics—with a small proportional charge—much abuse would be avoided.
8. Alternatively, more complex agents could be available only privately.

John Sterland MB BS

24 November 1997

Memorandum by EJ Sweeney PHD, Dip Bact, MRCVS

BACTERIAL RESPONSES TO ANTIBIOTICS

Judging by the published literature there would appear to exist a widespread belief that the role played by antibiotic agents in determining the now-familiar increased frequency of isolation of antibiotic-resistant pathogenic bacteria in man and domestic animals is limited to providing a means for resistant organisms to escape the potentially competitive influence of sensitive cohabitants. The reality, however, is that the notion of attributing a purely passive role to antibiotic agents accords little, if at all, with a number of crucial facts well known to medical (human and veterinary) investigators. There exists a large volume of independent evidence, for example, that where bacterial resistance follows exposure to antibiotics, the associated propensity for communicability (spread within and among communities) is still retained in the circumstance of antibiotic-free environments.^{1,3,5,14}

Moreover, the degree of communicability which is displayed by bacteria in association with exposure to antibiotics^{1,3,5,14} is vastly greater than that which is observable in ecologically comparable organisms in situations where there is no known history of antibiotic presence.^{2,6,7,8,13,15} The phenomenon popularly referred to as “antibiotic resistance” is difficult to explain therefore except by postulating that antibiotic presence may lead to the de-novo emergence of resistant mutants and that the basic species (mutator) propensity for adapting to environment may be enhanced as a legacy of antibiotic-induced mutation. The fact that the *in-vitro* action of antibiotics is in certain instances manifestly mutagenic, as in the case of the

effect produced by erythromycin on staphylococcus⁴ substantiates a hypothesis that the increased frequency of isolation of resistant organisms is in reality a consequence of the de-novo emergence of a highly communicable sub-population.

CONCLUSIONS

Rather than viewing "*bacterial resistance to antibiotics*" as causing a specific problem in the area of implementing effective control measures for diseases, the now-obvious confusion in literature pertaining to the mode of antibiotic action should be highlighted as an effect of a much more serious cause, namely the propagation of neodarwinism, a misleading brand of philosophy espoused by 19th Century Weismannist followers of Charles Darwin. By using any one of several readily available study models (mammalian as well as bacterial) it is not unduly difficult at the present time to produce testable evidence that the life process is essentially Lamarckian.^{10,11,12} So great is the potential for social and economic damage which is inherent in neodarwinism that it would be prudent at the present time to have "*resistance to antibiotics*" perceived as just a single problem in the context of overall difficulties created by existing communication conventions. The shortcomings of the peer-review factor in present-day conventions pertaining to science communications (by journals) are well known⁹ and the time may indeed be ripe for a fundamental reviewing of the role of peer reviewing in material being submitted for publication to journals.

REFERENCES

- 1 Bulling, E and Stephan, R. Studies on Transmissible Antibiotic Resistance in Enteric Bacteria. ZBL Vet Med B17: 121-124, 1970.
- 2 Craven, JA and Barnum, DA Ecology of Intestinal Escherichia Coli in Pigs. Canad J Comp Med. 35, No 4: 324-331, 1971.
- 3 Damato, JJ, Eitzman, DV and Baer, H. Persistence and Dissemination in the Community of R-factors of nosocomial origin. J Infect Dis 129, No 2: 205-209, 1974.
- 4 Garrod, LP. The Erythromycin Group of Antibiotics. Br Med J 2: 57-63, 1957.
- 5 Larsen, JL and Larsen, HE. Distribution and Persistence of Drug Resistant E. coli in Swine Herds with Intermittent use of Antibiotics. Nord Vet Med 26: 417-429, 1974.
- 6 Sears, HJ and Brownlee, I. Further Observations on the Persistence of Individual Strains of E. coli in the Intestinal Tract of Man. J Bact 63: 47 et seq, 1952.
- 7 Sears, HJ, Brownlee, I and Uchiyama, JK. Persistence of Individual Strains of E. coli in the Intestinal Tract of Man. J Bact 59: 293 et seq, 1950.
- 8 Sears, HJ, Janes, H, Saloom, R, Brownlee, I and Lamoreaux, LF. Persistence of Individual strains of E. coli in man and dog under varying conditions. J Bact 71: 370 et seq, 1956.
- 9 Smith, R. Peer Review: Reform or Revolution? Br Med J 315: 759-760, 1997.
- 10 Sweeney, EJ. Mechanisms of Mutation: A Perception from Mutation in Bacteria. Irish Vet News March: 38, 1985.
- 11 Sweeney, EJ. A Study of Evolutionary Mechanisms Modelled on Mutation in Bacteria. Vet News 9 No 7: 13-19, 1987.
- 12 Sweeney, EJ. Mammalian Models for Use in the Study of Ageing. Irish Vet News 11, No 4: 16-19, 1989.
- 13 Wallick, H and Stuart CA. Antigenic Relationships of Escherichia Coli isolated from one individual. J Bact 45: 121-126, 1943.
- 14 Williams Smith, H. Transfer of Antibiotic Resistance from Animal and Human Strains of Escherichia Coli to Resident E coli in the Alimentary Tract of Man. Lancet 1: 1174-1176, 1969.
- 15 Williams Smith, H and Crabb, WE. The Typing of Escherichia Coli by Bacteriophage: Its application in the study of the E Coli Population of the Intestinal Tract of Healthy Calves and of Calves Suffering from White Scours. J Gen Microbiol 15: 556 et seq, 1956.

Memorandum by Dr David Tyrrell

1. It is worrying that there has been a steady increase in the frequency and degree of resistance of more and more pathogens of man against more and more antibiotics and other antimicrobial agents. Furthermore, as the organisms are studied it becomes clear that this resistance comes from a variety of sources ranging from random mutations in the genes controlling the targets of the agents to the transfer of groups of resistance factors from distantly related organisms. Yet there is a simple underlying theme to these apparently diverse findings. This is that microbes,—and for this purpose we can include viruses, fungi and protozoa with the pathogenic bacteria—belong to immensely diverse and ancient life forms that have survived for hundreds of millions of years during which the physical and biological environment of the planet have changed enormously and repeatedly. Many changes has exerted a selection pressure on the organisms and in response they have adapted and evolved to overcome the adverse effects on their replication and persistence. As a result their descendants are still here though so many higher forms of life have come and gone.

2. We have seen the response of these organisms to the selective pressure of the drugs we have added to their environment already and there seems to be no reason why this should not continue if we employ more drugs in the future. There may be differences in the speed with which this occurs and because sometimes it takes place slowly some people have been misled into thinking that it would not happen—as in the case of resistance of pneumococci to penicillin. But we should remember that for organisms that have survived during aeons of time to develop a resistance mechanism in a few decades is actually responding rather quickly.

3. By applying these simple biological ideas we can shape a policy to reduce the development of resistance and the serious present and future problems that it indicates. Firstly, avoid using the drugs when they will do no good—for example, antibiotics in common colds—and may have adverse effects. Secondly, avoid the spread of resistant organisms from patients under treatment—for example, applying careful hand washing and in some cases room isolation of treated patients who are shedding organisms. Thirdly, new drugs should be designed to attack molecular targets that are different from those of present drugs, because in due course they will be needed. Fourthly, try the effect of a policy of changing the commonly used antibacterial every year or so; this apparently helps in relatively small countries and an administrative/biological experiment would be worth trying here. The switch could not be complete but as the resistant strains may be at a biological disadvantage they may decline in prevalence under such a regime. Finally, encourage methods of dealing with infections that do not use selective drugs—using cytokines to control soft tissue infection in diabetes is an example.

4. There are many ways in which help can be given—physicians, nurses and administrators as well as the microbiologists and pharmaceutical teams. Patients should not be forgotten as they often expect a prescription of an antibiotic for a common cold. This would be greatly supported by a statement from the Select Committee on the nature and the seriousness of the problem and the broad terms in which it can be understood and methods of control can be undertaken.

BIOGRAPHICAL NOTE

I was trained in clinical medicine and virology and after preliminary training was employed by the Medical Research Council. As a consultant Physician and Head of the Division of Communicable Diseases I was part of the team that set up the Clinical Research Centre at Northwick Park Hospital, Harrow and served on the Control of Infection Committee as well as running the Common Cold Unit at Salisbury for many years. I have published work on the spread of infection and the resistance of viruses to antiviral drugs.

Dr David Tyrrell

24 September 1997

Memorandum by Dr G Ulmanis

I would like to submit the following points for [possible] discussion by members of the Sub-Committee on resistance to Antimicrobial Agents.

1. In Sheffield, as in many other cities, hospitals are undergoing rationalisation to improve efficiency, reduce duplication and so bring cost cutting benefits to the NHS. For instance, we now have only one adult 24hr A and E unit [and a separate children's A and E unit] and more and more medical departments are being moved from other Sheffield hospitals to one site at the Northern General Hospital. But in doing so isn't there a risk that if "hospital infections" get out of hand not only wards may be closed but the whole viability of a hospital and with it the entire medical facilities of a city?

I realise that this is undoubtedly alarmist but surely this may be one outcome of centralising all [or most] of a city's medical facilities into one unit?

Before antibiotics became available, the medical community coped, or at least tried to cope with epidemics by using isolation units often on the edges of our cities. As these are either mothballed or sold off, isn't one line of defence against new antibiotic resistant infections lost to us?

2. The use of viral bacteriophages have been shown in the former Soviet Union to be extremely effective against many bacteria and the infections caused by them, but it seems this line of research has had little money and time spent on it in the UK. Rather than only putting more and more money into research on new antibiotics, which by the time they are produced may already have organisms showing resistance to them, wouldn't it be wise for the relevant Government organisations to at least look at bacteriophages and support any ongoing research on these?

Are drug companies too concerned with potential revenues for new antibiotics to follow other lines of research—simply because they are viewed as being unprofitable?

Dr G Ulmanis

19 December 1997

Memorandum by the United Kingdom Agricultural Supply Trade Association

INTRODUCTION

1. The United Kingdom Agricultural Supply Trade Association Ltd. (UKASTA) represents manufacturers, processors, distributors, traders and brokers of animal feedingstuffs, grain, pulses, seeds, fertilisers, plant protection chemicals and other goods and services used in the agricultural and horticultural industries.

2. In the context of this submission, our comments relate particularly to the interests of our members involved in the animal feed sector, who supply livestock producers with one of their most important inputs.

3. It is estimated that approximately 16 million tonnes of compound feedingstuffs is fed annually to UK farm livestock. Of this total, approximately 14 million tonnes is manufactured by either commercial feed compounders or integrated poultry producers (for detailed statistics please see Tables 1 and 2). The vast majority of these manufacturers are members of UKASTA. The remaining two million tonnes of feed is manufactured by on-farm mixers. Ruminant and some monogastric animals also consume forages and some straight feedingstuffs including home-grown cereals and root crops which, it is estimated, would amount to several million tonnes a year. (For a definition of the different types of feedingstuffs and additives, please see Appendix A).

BACKGROUND

4. In 1969 the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (the Swann Committee) published its report (Anonymous, 1969). One of its recommendations was that medicines used for control of human diseases should not be used as growth promoters in animal production and, where possible, different medicines should be used for human and animal disease control. Since the publication of that report UKASTA has worked in conjunction with the Ministry of Agriculture, Fisheries and Food (MAFF), the Veterinary Medicines Directorate (VMD) and the enforcement authorities which include inspectors from the Royal Pharmaceutical Society of Great Britain (RPSGB) and Department of Agriculture for Northern Ireland (DANI) in the development of the legislation relating to the manufacture of medicated feedingstuffs.

5. In the early 1980's UKASTA produced a Cross-Contamination Code of Practice which provided guidelines for the manufacture of medicated feedingstuffs. This was circulated to members and it has been in operation for approximately 16 years. In 1988–89 new legislation was brought into force by MAFF governing the manufacture, sale and supply of medicated feedingstuffs. An important part of the new regulations was the requirement for all manufacturers who incorporated medicinal products in feed, including supplements and protein concentrates, to belong to a Register of approved manufacturers. The Register is divided into two groups which are, respectively, Category A and Category B.

6. MAFF published in 1987 two Codes of Practices for manufacturers on Category A or B, these Codes were revised in 1991. (MAFF Publications, 1991). UKASTA was consulted in the drafting of the Code of Practice for Category A manufacturers. Inspectors from the RPSGB and DANI visit feed mills, on average, once a year to check compliance with the legislation and Code of Practice. Although these Codes were central to the legislation on the manufacture of medicated animal feedingstuffs, they did not contain sections on the operational aspects of manufacturing medicated feedingstuffs ie diets containing POM* and/or PML* medicinal additives. In the later 1980's UKASTA therefore revised the Cross-Contamination Code of Practice and produced its "Guidelines for the Manufacture of Medicated Animal Feedingstuffs". This document was further revised in full consultation with the VMD and the enforcement authorities in 1996. (A copy of the latest version of the "Guidelines for the Manufacture of Medicated Animal Feedingstuffs" is enclosed). (*not printed*)

7. In 1991 the Government set up the Expert Group on Animal Feedingstuffs under the Chairmanship of Professor Eric Lamming. UKASTA co-operated fully with the Expert Group by submitting a written report and giving verbal evidence on two occasions. The first was a presentation on the feed legislation associated with BSE and salmonella and the second on the regulations covering the manufacture, sale and supply of feedingstuffs under the Medicines Act 1968 and the Agriculture Act 1970. Subsequent to these presentations, UKASTA put forward views on the establishment of "The level playing field". This proposed that all sectors of the feed industry be subject to the same legislation. (A copy of an updated version of this paper is attached as Appendix B). The Association welcomed the publication of the Lamming Report (Anonymous, 1992) in July 1992.

- POM—Prescription Only Medicine.
- PML—Pharmacy and Merchants' List Additives.

N.B. The VMD is currently reviewing the legislation governing medicated feedingstuffs and zootechnical feed additives. The aim is to release zootechnical additives, namely antibiotic growth promoters, coccidiostats and other medicinal substances, and chemical growth promoters from the need, under the terms of the Medicines Act, to seek Product Licences.

8. UKASTA submitted written evidence and in April 1994 gave a verbal presentation to the Advisory

Committee on the Microbiological Safety of Food (ACMSF) Working Group on Poultry Meat. The Association endorsed the recommendations subsequently published by the Working Group in its Report on Poultry Meat (Anonymous, 1996). UKASTA noted that feed members had been paying full attention to the MAFF Codes of Practice for the control of salmonella in raw materials and finished feed since their introduction in 1989. Also, for some considerable time feed manufacturing members had been involved in precisely the sort of upgrading of equipment and facilities recommended by the Working Group. The Association was also keen to ensure that high hygiene standards were consistently achieved and maintained so that the feed industry would be playing its part, alongside other sections of the poultry production, processing and distribution chain, in improving the microbiological status of UK poultry meat.

9. UKASTA recognises that the question of antibiotic resistance is a worldwide problem and is one in which UK Ministers are taking a keen interest. In February 1997, the Association submitted written evidence to the ACMSF Working Group on Antimicrobial Antibiotic Resistance in Relation to Food Safety. On 9 September, representatives of the Association gave oral evidence to the Working Group.

10. UKASTA also fully supports the intention of Government to ensure that the food the nation's population buys is safe to eat. UKASTA is, therefore, developing a Feed Assurance Scheme which is taking on many requirements of current and pending legislation as well as other aspects which go beyond statutory control. At the same time we aim to provide members with practical guidance on the manufacture of safe animal feedingstuffs. UKASTA considers that it is essential that these provisions be extended to cover all routes through which feed is fed to UK farmed livestock. The scheme, which will be voluntary, will, hopefully, be implemented by the industry during the course of 1998.

PRACTICAL EXPERIENCE

(a) *Veterinary Medicinal Residues in Pigmeat*

11. During 1995 representatives of UKASTA, together with officials from the VMD, Central Veterinary Laboratory (CVL) and State Veterinary Services (SVS) were involved in investigations into the source of sulphonamide residues in pig meat. This exercise arose further to requests for assistance from a large pig slaughterhouse which had had some consignments of pig meat exported to the Far East rejected.

12. The conclusions of the investigations, which were reported by VMD in January 1996 (VMD Publications 1996), indicated that the sulphonamide residue problem could be due to a combination of factors namely:

- (a) deficiencies in the safe handling and usage of veterinary medicines and medicated feedingstuffs on farm;
- (b) increased use of sulphonamide medicated feedingstuffs due to the increased level of respiratory disease occurring in intensively reared pigs;
- (c) low level cross-contamination in feedingstuffs; and
- (d) cross-contamination between medicated and non-medicated pigs on farm, during transport and in the lairage at the abattoir.

13. In the report on the investigations the authorities stated that there was no simple answer to the problem of sulphonamide residues but a number of actions were identified which could be taken to reduce the problem. These included the revision of the Codes of Practice for Category A and B registered manufacturers of medicated animal feedingstuffs. This was to be done in conjunction with UKASTA and the RPSGB to stress the importance of avoiding cross-contamination of feeds with POM products during the manufacturing process and during the transport and delivery of medicated feedingstuffs to farms.

14. Following publication of this report and as previously stated in paragraph 6, UKASTA further revised its Guidelines for the Manufacture of Medicated Animal Feedingstuffs in 1996. As before, the aim in revising the document was to enable registered manufacturers to comply with the legislation on the manufacture of medicated feedingstuffs and to minimise the risk of the feed route being the source of medicinal residues in human food. The revised document was sent to the VMD, RPSGB and DANI for comment prior to its publication in mid 1996 and circulation to all feed members of UKASTA.

15. UKASTA awaits publication of the revised Codes of Practice for manufacturers on Categories A and B by the VMD having commented on the drafts some months ago.

(b) *Veterinary Medicinal Residues in Eggs*

16. The VMD publishes quarterly data on residues monitoring in the Medicines Act Veterinary Information Service (MAVIS) (VMD Publications). These report on the two complementary surveillance programmes operated by the VMD. The National Surveillance Scheme for residues in meat is a statutory programme designed to monitor whether residues of veterinary medicines are passing into meat for human consumption in an acceptable concentration. The second is a non statutory programme supplementing the statutory one and extending to analyte/matrix combinations not covered by it. UKASTA monitors the

information published in these reports and discusses any points of concern with the VMD and other interested bodies.

17. In 1995 attention focused on the isolation of lasalocid residues in eggs. Following discussions between the VMD and the pharmaceutical company producing lasalocid, the product's physical form was changed as concern had been expressed that its fine powdery nature might have been leading to holdups in the mill and thus the possibility of this medicinal additive finding its way into rations for laying hens. On the introduction of a more granular presentation of lasalocid it was noticeable that its residue in eggs virtually disappeared.

18. More recently, the industry has been concerned at the identification of nicarbazin residues in eggs. It is, therefore, currently considering whether the physical form of this medicinal additive has any influence on the potential for holdup in the mill and thus trace quantities entering layer feedingstuffs. In reporting these results in MAVIS, the VMD has stated that whilst the concentrations being found are not considered to pose a health risk to consumers, the substance is not licensed for use in laying hens. Discussions are currently being held between representatives of the egg industry, UKASTA and the VMD on these reported findings.

(c) *Statistics on the use of feed additives in animal feedingstuffs*

19. Table 3 (attached) indicates the use of medicines under Veterinary Written Direction (VWD) in feedingstuffs for the main categories of UK farmed livestock. It also covers the use of PML additives in ruminant feedingstuffs but excludes the addition of zinc oxide and copper sulphate.

20. The main prescription only medicines which are incorporated into feedingstuffs for the different classes of farm livestock, under Veterinary Written Direction (VWD), are as follows:

Pigs—penicillins, chlortetracyclines, lincomycin, sulphonamides, tiamulin, dimetridazole and zinc oxide.

Poultry—penicillins, chlortetracycline, oxytetracyclines and sulphonamides.

Cattle—these are prescribed mainly for young calves and include chlortetracyclines and oxytetracyclines.

Sheep—monensin.

These products are essential for the health and welfare of farm livestock in existing husbandry methods.

21. The main PML (i.e. Pharmacy and Merchants List) feed additives which are incorporated into feedingstuffs for the different classes of farm livestock are as follows:

Pigs—virginiamycin, tylosin, avilamycin, salinomycin, zinc bacitracin and copper sulphate.

Poultry—virginiamycin, zinc bacitracin, lasalocid, nicarbazin, monensin, salinomycin, narasin, clopidol, methylbenzoate, dimetridazole and nifursol.

Cattle—monensin and virginiamycin.

22. Legislation was brought into effect in the UK to implement the Swann Committee recommendation that medicines used for control of human diseases should not be used as growth promoters in animal production. These controls, which have been amended over the years, were underpinned when the UK became a member of the European Community as legislation made under the EC Additives Directive was brought into operation. This Directive lists the specific products, referred to as zootechnical feed additives, which have been authorised as antibiotics (Group A); or coccidiostats and other medicinal substances (Group D); or growth promoters (Group J). (A list of the zootechnical feed additives, authorised under the EC Additives Directive is attached as Appendix C). If the use of these zootechnical feed additives were not permitted it is expected that the use of POM products would increase. (A list of current legislation, covering the manufacture and sale of both medicated and non-medicated feedingstuffs is set out as Appendix D).

(d) *Antibiotic Resistance*

23. From 1990–96 the total number of salmonellas in human beings in the United Kingdom referred annually to, respectively, the Public Health Laboratory Service (PHLS), Scottish Centre for Infection and Environmental Health and DHSS (NI) is about 33,500. In 1996, about 6,500 of these isolations were of *Salmonella typhimurium*. An important factor in this increase, which started in 1990, had been an epidemic of multi-drug resistance *Salmonella typhimurium* DT104.

24. Since 1990, isolates of *S. typhimurium* DT104 with resistance to ampicillin (A), chloramphenicol (C), streptomycin (S), sulphonamides (Su) and tetracyclines (T) (= R-type ACSSuT) have predominated in human beings. Since 1994, it has also been reported that isolates of multi-resistant *S. typhimurium* DT104 with additional resistance to trimethoprim (R-type ACSSuTTm) or to ciprofloxacin (R-type ACSSuTCp) have increased in incidence. In 1996 21 per cent of *S. typhimurium* DT104 isolates from human beings were of R-type ACSSuTTm and 13 per cent were of R-type ACSSuTCp or ACSSuTTmCp.

25. It should be noted that all the antimicrobials mentioned above are only available for the treatment of animals under veterinary prescription. Only three of these antimicrobials can be prescribed for incorporation

into feedingstuffs under a VWD i.e. sulphonamides, tetracyclines and trimethoprim. However, they will not be used via this route in ruminating animals because of their adverse effect on rumen bacteria.

26. The Central Veterinary Laboratory also reported that *S. typhimurium* DT104 R-type ACSSuT had become increasingly common in cattle in England, Wales and Scotland. The organism had also been isolated from other food animals including poultry, sheep and pigs.

27. As reported by MAFF, *S. typhimurium* is rarely found in animal feedingstuffs. Table 4 sets out recent MAFF statistics on the isolation of *S. typhimurium* and *S. enteritidis* in animal feedingstuffs.

28. UKASTA was instrumental in the drafting of the Ministry's 1989 Code of Practice for the control of salmonella in animal feedingstuffs. This was subsequently revised in full consultation with interested organisations by MAFF and circulated to members of the feed industry. MAFF produced three Codes of Practice directly applicable to animal feedingstuffs which are:

- Code of Practice for the control of salmonella during the storage, handling and transport of raw materials intended for incorporation into or direct use as, animal feedingstuffs (MAFF Publications 1995 PB 2202).
- Code of Practice for the control of salmonella in the production of final feed for livestock in premises producing over 10,000 tonnes per annum (MAFF Publications 1995 PB 2200).
- Code of Practice for the control of salmonella in the production of final feed for livestock in premises producing less than 10,000 tonnes per annum (MAFF Publications 1995 PB 2201).

29. As with the initial documents produced in 1989, these Codes of Practice formalise procedures within the feed industry designed to minimise the risk of animal feedingstuffs being vectors for introducing salmonella and other pathogens into the food chain.

30. In addition, MAFF produced Codes of Practice for the control of salmonella in protein meals, produced from raw materials of fish, animal or poultry origin and intended for use as raw materials in the feed industry. These were for the UK fish meal industry and the animal by-products rendering industry; however, since 29 March 1996 the use of mammalian meat and bone meal has been banned in feed for all farmed livestock (MAFF, 1996). The MAFF also produced Codes of Practice for the control of salmonella in the poultry industry.

(e) Other Zoonotic Problems

31. UKASTA constantly monitors the media for any reference, however tenuous, to the animal feed route being a vector for disease organisms. For instance in the case of *Escherichia coli* 0157, and before the Lanarkshire outbreak, we had discussed the possibility of this bacteria being transmitted by feed. Our understanding is that the pattern of inhibition, growth requirements and destruction of *E. coli* by heat treatment and the use of chemical processing aids, are generally similar to those of other enterobacteriaceae such as salmonella. Hence, production processes that control salmonella will probably also control *E. coli* serotypes. We understand that the incidence of multi-drug resistance in *E. coli* 0157 is at a low level (Willshaw *et al.* 1996).

CONCLUSIONS

32. UKASTA's interest in this submission is the role played by medicinal feed additives which are an important and, in some circumstances, an essential part of the animal production chain. The POM additives are incorporated into feedingstuffs for farmer customers only when prescribed by their veterinary surgeons to control disease and alleviate unnecessary suffering of animals under their direct care. Only medicines authorised for use in animal feedingstuffs are used. All medicines are subject to statutory withdrawal periods to reduce to a minimum the possibility of residues occurring in livestock products. UKASTA fully supports international controls throughout the European Union and third countries to ensure that foodstuffs entering the human food chain are wholesome and of a high quality as well as produced under equitable and economic production systems.

33. The PML additives are incorporated into animal feedingstuffs in accordance with their marketing authorisations/product licences. The blackhead and anticoccidial additives are used for disease prevention to minimise animal suffering and until alternative means of control are developed are essential for animal welfare. The growth promoters, which are mainly gut active and thus usually show no, or very low, levels of tissue retention, enable animals to utilise their diet more effectively. In this way they reduce the amount of waste excreted, by improving feed utilisation and thus are beneficial to the environment.

34. It follows that the removal of growth promoters would have an impact on the environment. For example it has been estimated that their removal from pig feedingstuffs would have the following effect in the United Kingdom:

- 6-12 per cent increase in pig meat production cost;
- 126,000 tonnes feed extra;
- 13,000 lorry movements extra;
- 63,000 tonnes wheat extra;
- 133,000,000 gallons of slurry extra;
- 26,000 tonnes of nitrogen extra; and
- 410 million cu metres methane extra.

35. As already stated, the animal feed industry has had formalised procedures in place over the last 16 years on the manufacture of medicated feedingstuffs and the avoidance of medicinal residues in human foods. Also, with the adoption of the salmonella Codes of Practice, the feed industry has for the past eight years been following procedures designed to minimise the risk of introducing salmonella and other pathogens into the food chain. Furthermore, over the last few years the industry has been considering the design of feed mills to improve hygiene within them, this being one of the recommendations of the Advisory Committee on Microbiological Safety of Food.

36. UKASTA recognises that even after the control measures already introduced, potential problems may still be associated with the use of medicinal feed additives. These include veterinary medicinal residues being detected at very low levels and possible links between some POM antibiotics and bacterial resistance. However, our consultations lead us to believe that in many instances the feed route is the best one for the administration of these products. The Association would obviously be concerned if the use of individual medicinal feed additives led to the development of bacteria resistant to the therapeutic antibiotics prescribed for use in human beings. We are aware of suggestions that the use of antimicrobials in human medicine is a significant cause of antibiotic resistance and that some multi-resistant strains may already be well established. We are not in a position to evaluate these suggestions but it is clear that an expert and critical assessment of the use and value of antimicrobials in human medicine is desirable.

October 1997

REFERENCES

- Anonymous, (1969). *Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine*. London: HMSO.
- Anonymous, (1992). *Report of the Expert Group on Animal Feedingstuffs*. London: HMSO.
- Anonymous, (1996). *Report of the Advisory Committee on the Microbiological Safety of Food Working Group on Poultry Meat*. London: HMSO.
- MAFF Publications, (1991). *Code of Practice for Category A registered manufacturers of medicated animal feedingstuffs*. PB 0766.
- MAFF Publications (1991). *Code of Practice for Category B registered manufacturers of medicated animal feedingstuffs*. PB 0767.
- MAFF, (1996). *The Bovine Spongiform Encephalopathy (No. 2) Order 1996* (SI. 1996/No. 3183).
- VMD Publication, (1996). *Report of the investigations into the source of sulphonamide residues in pig meat*. VMD.
- VMD Publication. *Medicines Act Veterinary Information Service*. VMD.
- Willshaw, G A, Cheasty, T, Frost, J A, Threlfall, E J and Rowe, B. *Notiziario dell'Istituto Superiore di Sanita*, Vol 9, N. 11 (Suppl 3) 1996.

Table 1
COMPOUND FEED OUTPUT—UNITED KINGDOM

<i>Feed Output Thousand Tonnes)</i>	<i>1990</i>	<i>1991</i>	<i>1992</i>	<i>1993</i>	<i>1994</i>	<i>1995</i>	<i>1996</i>
Calf Milk Replacers	23.2	24.2	29.0	28.5	28.1	22.3	20.3
Other Calf Feeds	292.1	249.6	205.4	224.3	249.9	275.8	243.8
Total Calf Feeds	315.3	273.8	234.4	252.8	278.0	298.2	263.9
Dairy Feeds	3,074.3	2,938.7	3,140.6	3,264.4	3,213.9	3,195.1	3,052.7
Other Cattle Feeds	688.9	727.3	797.6	838.5	959.6	1,100.0	1,168.3
Protein Concentrates	97.4	93.9	93.5	95.3	93.0	107.7	112.4
Total Cattle Feeds	3,860.6	3,759.9	4,031.7	4,198.2	4,266.5	4,403.8	4,333.4
Total Cattle and Calf Feeds	4,175.9	4,033.7	4,266.1	4,451.0	4,544.5	4,702.0	4,597.3
Pig Starters and Creep Feeds	182.4	203.9	162.5	164.5	158.5	161.4	163.2
Pig Growing Feeds	n/a	n/a	n/a	653.3	653.6	580.1	600.0
Pig Finishing Feeds	n/a	n/a	n/a	881.5	911.3	942.4	988.9
Pig Breeding Feeds	677.5	693.2	745.3	779.4	748.0	699.1	739.7
Other Pig Feeds	1,367.7	1,403.5	1,504.6	n/a	n/a	n/a	n/a
Protein Concentrates	61.3	52.2	52.9	51.4	47.9	38.7	41.3
Total Pig Feeds	2,288.9	2,352.8	2,465.3	2,530.1	2,519.3	2,422.1	2,533.1
Layer Feeds	951.6	942.3	898.3	885.0	893.3	895.5	932.3
Broiler Feeds	1,702.3	1,761.9	1,693.3	1,652.1	1,662.8	1,684.5	1,748.7
Turkey Feeds	634.8	629.6	597.8	632.9	661.3	765.8	746.7
Other Poultry Feeds (a)	536.8	518.9	582.2	596.4	639.9	641.7	654.0
Protein Concentrates (GB only)	31.7	12.9	12.1	12.7	12.2	8.8	8.2
Total Poultry Feeds	3,857.2	3,865.6	3,783.7	3,779.1	3,869.3	3,996.3	4,089.9
Breeding Sheep	n/a	n/a	n/a	360.8	404.6	408.8	463.5
Grower/Finisher Feeds	n/a	n/a	n/a	166.8	212.6	251.0	248.7
Protein Concentrates	n/a	n/a	n/a	5.9	6.3	9.8	9.6
Total Sheep and Lamb Feeds	531.6	569.2	564.7	533.5	623.5	669.6	721.8
Total miscellaneous Feeds inc. horse and fish feeds	324.0	289.7	350.4	378.6	399.2	443.5	485.9
Total Compounds	11,178	11,111	11,430	11,672	11,956	12,233	12,428

(a) Other poultry feed includes breeding and rearing diets in Great Britain and protein concentrates in both Great Britain and Northern Ireland.

Source: MAFF and DANI Returns. Updated Q3 96

Table 2
INTEGRATED POULTRY FEED PRODUCTION
RAW MATERIAL USAGE (THOUSAND TONNES)

	<i>1990-91</i>	<i>1991-92</i>	<i>1992-93</i>	<i>1993-94</i>	<i>1994-95</i>	<i>1995-96</i>
Wheat	901	817	874	962	984	935
Barley	119	216	192	162	136	221
Maize	3		2	2		
Other Grains	6	5	4	3	10	2
Total Grains	1,028	1,037	1,071	1,130	1,157	1,158
Estimated Other Materials ⁽¹⁾	613	710	813	843	810	829

FEED PRODUCTION (THOUSAND TONNES)

	1990-91	1991-92	1992-93	1993-94	1994-95	1995-96
Broiler Chicken	932	951	966	1,012	1,025	1,046
Turkey Feeds	243	258	295	309	333	337
Layer Feeds	314	321	361	388	349	344
Breeding and Rearing Feeds	130	112	123	142	153	154
Other Poultry Compounds		1	8	3	2	1
Protein Concentrates	22	104	131	119	105	105
Total Compounds	1,641	1,747	1,884	1,973	1,967	1,987

Note: Only including integrated producers who do not report production in the survey of compound feed output.

⁽¹⁾ No data is supplied for use of other than grain by integrated producers. The figure thus represents total feed production less usage of grain.

Source: MAFF Revised and Updated Q3 96.

Table 3

	<i>Total Tonnage*</i> 1996 (Thousand Tonnes)	<i>Total Tonnage</i> with VWD 1995 %	<i>Total Tonnage</i> with PML %
PIGS			
Starters	163.2	45-55	Circa 100*
Weaners			
Grower	600.0	35-45	Circa 100*
Finisher	988.9	15-25	Circa 100*
Breeder	739.7	10-15	Circa 0
*includes copper sulphate.			
POULTRY			
Broiler Starter	349.7	15-25	100
Broiler grower	1,399.0	less than 5	100
Broiler finisher*			
Turkey Starter	746.7	less than 5	100
Turkey grower			
Turkey finisher*			
Chicken starter	145.2	less than 5	Circa 80
Other poultry (eg duck, geese & game)	324.5		Circa 50
Layers for egg production	932.3	less than 1	0
Breeder/rearer	384.3	less than 5	Circa 70

*There are withdrawal feeds made available which do not contain anticoccidiostats or antiblackhead additives but may contain growth promoters for which the withdrawal period is nil.

CATTLE

Calf Starter	263.9		Very little used
Cattle grower	1,168.3	less than 0.5	more than 80%
Dairy	3,052.7	0	0*

* excludes copper sulphate needed to correct mineral deficiency.

SHEEP

Lamb starter			
Lamb grower	721.8	less than 2	less than 2
Lamb finisher			
Ewe			

This covers most but not all feeds listed in Table 1.

Please note that for some of the above categories whilst the figures given are our best estimates some companies did report higher figures.

Table 4

1. TESTS BEING PERFORMED ON FEEDINGSTUFFS AND INGREDIENTS, 1996

<i>Product</i>	<i>No of tests</i>	<i>No of tests positive</i>	<i>Per cent positive</i>
Processed animal protein at a GB protein processing premises	10,023	317	3.2
GB and imported processed animal protein arriving for feedingstuffs use	2,927	126	4.3
Linseed meal, rapeseed meal, soyabean meal and sunflower meal at a UK crushing premises	4,155	250	6.0
All other tests on oilseed meals and products for feedingstuffs use	14,564	604	4.1
Non-oilseed meal vegetable products	14,091	243	1.7
*Pig and poultry meals	5,712	252	4.4
*Poultry extrusions	8,870	170	1.9
*Pig extrusions	3,874	42	1.1
Ruminant concentrates	4,205	102	2.4
Protein concentrates	1,513	64	4.2
Minerals/other	1,037	44	4.2

*This table shows the results of tests on animal feedingstuffs and ingredients being performed under the Processed Animal Protein Order 1989 and MAFF Codes of Practice¹ at laboratories authorised under the Processed Animal Protein Order 1989.

2. ISOLATIONS OF *S. ENTERITIDIS* AND *S. TYPHIMURIUM* FROM ALL FEEDINGSTUFFS AND FEED INGREDIENTS BEING MONITORED UNDER MAFF CODES OF PRACTICE

<i>Type of material</i>	<i>1991</i>		<i>1992</i>		<i>1993</i>		<i>1994</i>		<i>1995</i>		<i>1996</i>	
	<i>Se</i>	<i>St</i>	<i>Se</i>	<i>St</i>	<i>Se</i>	<i>St</i>	<i>Se</i>	<i>St</i>	<i>Se</i>	<i>St</i>	<i>Se</i>	<i>St</i>
Finished feeds	0	15	6	15	5	9	4	25	2	20	0	18
Animal protein	24	0	0	0	0	1	0	4	0	1	0	10
Vegetable material	4	2	2	8	7	15	1	6	4	10	5	6
Minerals	0	0	0	0	0	0	0	0	0	0	0	0
Miscellaneous	0	0	2	5	2	1	0	4	1	5	1	2
Totals	28	17	10	28	14	26	5	39	7	36	6	36

¹MAFF, in consultation with industry, has issued Codes of Practice for the control of salmonella in the production of final feed for livestock; during the storage, handling and transport of raw materials intended for incorporation into animal feedingstuffs; and in the rendering and fishmeal industries. These Codes recommend testing for salmonella and have been widely adopted in Great Britain.

3. ISOLATIONS OF *S ENTERITIDIS* AND *S TYPHIMURIUM* FROM PRODUCTS MONITORED UNDER THE MAFF CODES OF PRACTICE, 1996

<i>Serotype</i>	<i>Feedingstuff</i>	<i>Number</i>
enteritidis	cotton	1
	rape	1
	wheat	2
	maize	1
	environmental	1
typhimurium	wheat	2
	soya	1
	barley	1
	rape	1
	maize	1
	meat and bonemeal	1
	fishmeal	9
	compound feed—pig	7
	compound feed—cattle	1
	compound feed—poultry	3
	unspecified	9

APPENDIX A

1. DEFINITIONS OF ANIMAL FEEDINGSTUFFS

The enormous advances in the development of scientific feeding of livestock, during the last 60 years or so, have led to a whole new range of feedingstuffs becoming available on the market. These provide the farmer with a range of options from which he can select the one most suited to his particular enterprise.

Arising from these developments, animal feedingstuffs terminology has become complex and, in some respects, a little confusing. The following definitions are an attempt to clarify the situation. It is stressed that they are not legal definitions but merely what is meant by the terms commonly used in the compound feed industry.

Compound Feeds

A number of different ingredients, including major minerals, trace elements, vitamins and other additives are blended and mixed in appropriate proportions to provide properly balanced diets for all types of livestock at every stage of growth and development.

In some cases, such as in ruminant feeding, compound feeds are designed without being mixed with cereals, to supplement the farmer's own feed resources. In such cases, compound feeds are frequently described specifically as designed to balance feeding with silage, straw, kale and the like.

Protein Concentrates

These are products specifically designed to be mixed, before being fed, at an inclusion rate of five per cent or more with predetermined proportions of cereals or other feedingstuffs. This process may be carried out either by livestock producers themselves or by a feed manufacturer.

Since the objective in this case is to ensure that the final ration which emerges after mixing is formulated for a particular feeding purpose, protein concentrates typically contain blended protein-rich ingredients such as fishmeal and soyameal, fortified with essential minerals, vitamins and trace elements.

In cases where the inclusion rate of protein concentrates to be used in the final diet is high—for example, over 50 per cent—they will contain some cereals or cereal by-products.

Straights

These are single material feedingstuffs of either vegetable or animal origin which may or may not have undergone some further processing prior to being sold.

Straights rarely provide, on their own, the complete nutritional requirements of livestock. Examples of straight feedingstuffs include wheat, barley, oil-cakes and meals and fishmeal.

Straight feeds are the raw materials from which all technically formulated feeds are prepared, whether mixed on the farm or manufactured in a compound feed mill.

Supplements

These are technical products, designed to comprise less than five per cent by volume of the ration in which they are to be included. Their purpose is to supply an appropriate level of vitamins, trace elements, non-nutrient additives and any other special ingredients.

To facilitate the mixing of such materials into the finished ration, appropriate levels of the active materials are normally designed to be present in the form of a supplement to a diluent carrier. Most supplements are available to both compound feed manufacturers and livestock producers.

Additives (including medicinal products)

Such additives include coccidiostats and anti-blackhead medications for mass prophylaxis or treatment on veterinary prescription, antibiotics for growth promotion, prophylaxis or treatment on veterinary prescription, antioxidants, colourings, flavourings and binders.

Source—Feed Facts Quarterly (HGM Publications)

APPENDIX B

THE LEVEL PLAYING FIELD

UKASTA considers that all animal feedingstuffs throughout the food supply chain should be subject to the same legislation. We see the supply chain as consisting of, inter alia:

- importers of materials from abroad, raw and processed;
- producers of raw materials within the UK, eg farmers and human food processors;
- processors of raw materials within the UK eg crushers;
- commercial compounders;
- integrated livestock producers making their own feed eg major poultry producers;
- on-farm mixers, using bought in farm-produced material; and
- users of feedingstuffs, be they:
 - compounds
 - home-mixed feed
 - farm produced or bought-in raw materials and straights.

Our view that legislation should be broadened from “sale and supply” of feedingstuffs to “sale, supply, manufacture, and use” reflects our opinion that the former description is now outdated and no longer covers the human food chain in total. Risks can clearly occur at any point, some of which are currently not subject to legislation.

UKASTA, furthermore recommends the establishment of an independent, centralised agency to be responsible for the enforcement of feedingstuffs legislation, and in particular, to cover aspects of safety and to monitor levels of undesirable substances. The Government should be responsible for deciding upon the Central Agency.

This agency could operate effectively as follows:

(i) *National Surveillance Plan*

The Central Agency would plan appropriate surveillance, on a national basis, of feedingstuffs at all stages of the chain. This may also fulfil EC obligations under legislation covering the manufacture, sale, supply and use of animal feedingstuffs.

(ii) Sampling

Sampling would take place at all points from port of entry, production and processing of raw material within the UK, manufacture, supply and on-farm use. Sampling would be in accordance with national guidelines.

(iii) Analysis of Samples

Routine analysis for nutritional declarations and medication should be done at local/regional level on a selection of sub samples from the total sampling exercise. The analysis for safety aspects, including undesirable substances, should be organised on a centralised basis in specialised laboratories who would receive all of the samples taken by the Central Agency under the national sampling operation. This could be parallel to the collection and analysis of samples of feedingstuffs. A number of these laboratories are already equipped with skilled staff and specialised instrumentation to handle large numbers of samples in a cost effective and speedy manner. Costs, therefore, should not be great.

(iv) Enforcement

The enforcement of the Regulations made under the Agriculture Act 1970 and the Medicines Act 1958 as well as the Orders under the Animal Health Act 1960 should be the responsibility of the Central Agency on the basis of the samples taken on the national surveillance plan. Consultation might also be given to bringing other legislation, with which the companies in the food supply chain have to comply, under the Central Agency.

(v) Co-ordination of Results

Centralised analyses for all undesirable substances would provide the authorities with a data base which would fulfil two important requirements:

- (a) Highlight any risks in the raw material/animal feedingstuffs/livestock production chain from the presence of toxic and other undesirable substances;
- (b) provide information for the targeting of resources so that corrective action can be applied effectively.

(vi) Manufacture of Medicated Feedingstuffs

The manufacturing and administration aspects of medicated feedingstuffs should be policed by the Central Agency.

(vii) Funding

To achieve an effective centralised agency and surveillance system, adequate funding must be provided and the options as to how this can be tackled have been considered most carefully. We believe that as the measures to be taken primarily concern the nation's health in general, costs should lie primarily with central government insofar as the Central Agency is concerned.

APPENDIX C

INDEX TO "MEDICINAL" ADDITIVES UNDER DIRECTIVE 70/524

ANNEX 1

Additive

Antibiotics (Group A)

Avilamycin
 Bacitracin zinc
 Flavophospholipol
 Monensin sodium
 Salinomycin sodium
 Spiramycin
 Tylosin phosphate
 Virginiamycin

Coccidiostats and Other Medicinal Substances (Group D)

Amprolium
 Amprolium/Ethopabate
 Arprinocid
 Decoquinate
 Diclazuril
 Dimetridazole
 Dinitolmide
 Halofuginone
 Ipronidazole
 Lasalocid sodium
 Maduramicin ammonium
 Meticlorpindol (clopidol)
 Meticlorpindol (clopidol)/methylbenzoate ("Lerbak")
 Monensin sodium
 Narasin
 Narasin/nicarbazin
 Nicarbazin
 Nifursol
 Robenidine
 Ronidazole
 Salinomycin sodium

Growth promoters (Group J)

Carbadox
 Olaquinox
 (Source: VMD)

APPENDIX D**THE AGRICULTURE ACT 1970, PART IV**

- (i) The Agriculture Act 1970 Amendment Regulations 1982 (S.I. 1982/No. 980).
- (ii) The Feeding Stuffs Regulations 1995 (as amended) (S.I. 1995/No. 1412).
- (iii) The Feeding Stuffs (Sampling and Analysis) Regulations 1982 (as amended) (S.I. 1982/No. 1144).

THE MEDICINES ACT 1968**THE ANIMAL HEALTH AND WELFARE ACT 1984**

- (i) The Medicines (Animal Feeding Stuffs) (Enforcement) Regulations 1985 (as amended) (S.I. 1985/No. 273).
- (ii) The Medicines (Labelling of Medicinal Products for Incorporation in Animal Feeding Stuffs and of Medicated Animal Feeding Stuffs) Regulations 1988 (S.I. 1988/No. 1009).
- (iii) The Medicines (Exemptions from Licences) (Intermediate Medicated Feeding Stuffs) Order 1989 (S.I. 1989/No. 2325).
- (iv) The Medicines (Intermediate Medicated Feeding Stuffs) Order 1989 (S.I. 1989/No. 2442).
- (v) The Medicines (Veterinary Drugs) (Prescription Only) Order 1991 (as amended) (S.I. 1991/No. 1392).
- (vi) The Medicines (Veterinary Drugs) (Pharmacy and Merchants' List) Order 1992 (as amended) (S.I. 1992/No. 33).

(vii) The Medicines (Medicated Animal Feeding Stuff) (No. 2) Regulations 1992 (as amended) (S.I. 1992/No. 1520).

(viii) The Medicines (Restrictions on the Administration of Veterinary Medicinal Products) Regulations 1994 (S.I. 1994/No. 2987).

THE ANIMAL HEALTH ACT 1981

(i) The Bovine Spongiform Encephalopathy (No. 2) Order 1996 (S.I. 1996/3183).

Memorandum by the UK National Committee for Microbiology

RESISTANCE TO ANTIMICROBIAL AGENTS—CAUSES AND CONSEQUENCES OF EMERGENCE

1. Even although it is estimated that over 99 per cent of all bacterial infections can still be treated by appropriate antibiotics, a number of species have developed significant resistance to our panoply of antibiotics—*Staphylococcus aureus*, *Mycobacterium tuberculosis*, enterococci and *Streptococcus pneumoniae*. In each case the development of resistance has necessitated the use of a more expensive and perhaps more toxic drug as a last line in therapy.

2. Antibiotic resistance has tended to arise within the hospital environment but its spread to nursing homes and the community has raised cause for concern. The increased resistance levels in hospitals appears to be linked to the use and misuse of antibiotics, as well as the degree of adherence of infection control procedures by hospital personnel. Antibiotic pressure tends to select more resistant organisms and if conditions whereby rapid spread is possible as in nurseries then the level of resistance can escalate rapidly as was seen in Iceland with penicillin-resistant pneumococci.

3. Another cause of the increase in drug resistance is recognised in developing countries where many antibiotics are available over the counter. This has led to widespread drug resistance in the community and in some situations concomitant HIV infection, large scale population movements, inadequate sanitation and poor medical care only exacerbates the situation. Drug resistant bacteria have also found their way into humans via the food chain especially where antibiotics have been used in animal husbandry as growth promoters rather than as therapy for infection.

4. These points have already been addressed many times in the literature yet it seems that insufficient importance is being placed on methodologies designed to reverse the changes in drug susceptibility taking place among bacterial pathogens leading to higher and higher levels of drug resistance. The high costs of drug development and the long delays in bringing new drugs to the market, coupled with increasing global levels of antibiotic resistance are widening the gap between the appearance of new strain(s) displaying new antibiotic resistance patterns and our ability to control them. Improved surveillance procedures will only be of benefit if secure and reliable antibiotic prescribing policies, better hygiene and control of infection procedures are in place.

5. Most hospital prescribing is done by junior staff who have limited experience in antibiotic therapy. Antibiotic policies usually restrict the number of agents available from a given antibiotic class; this reduces confusion, allows staff to gain expertise in a smaller number of drugs, helps preserve the effectiveness of newer agents and reduces pharmacy costs. Older, cheaper and well established “first line” antibiotics are unrestricted and can be prescribed by all staff for simple infections.

6. Even when an antibiotic prescription is justified, therapy may be unnecessarily prolonged. One way to reduce the length of treatment is to agree “stop” policies in which the pharmacy automatically cancels an antibiotic prescription after 3–5 days unless it is specifically renewed by the ward physician. A large proportion of antibiotic use and misuse is for prophylaxis, and it is especially important to have clear policies in this area. The hospital antibiotic committee should review the scientific literature in each area of prophylaxis, and issue guidelines for the choice of agent and the timing of administration. For most surgical prophylaxis the antibiotic should be given just before surgery and continue for no more than 24 hours. Limitation of prophylaxis in this way will greatly reduce the pressure on antibiotic resistance as well as producing considerable cost savings.

7. There is evidence in the literature that formal policies of rotation—or complete withdrawal—of certain antibiotics were useful in the past for dealing with the emergence of multi-resistant organisms. This type of policy was usually applied to problems of resistance in Gram-negative bacteria at a time when relatively few effective agents were available. Nowadays several antibiotic groups are active against Gram-negatives, and such policies are not often required. Nevertheless, in some areas where gentamicin resistance in enterobacteria and pseudomonas has been a problem, but where organisms have remained sensitive to amikacin, hospitals have adopted a policy of exclusive use of amikacin. In these centres this policy has resulted in a decrease in gentamicin resistance without a concomitant increase in amikacin resistance. However, most hospitals now find multiple resistant Gram-positive bacteria to be the major problem in hospital infection. There may be a need in the future to rotate or restrict agents active against Gram-positive bacteria in order to preserve the effectiveness of reserve drugs such as vancomycin.

8. Some of this antibiotic misuse results from inadequate knowledge and poor understanding of antimicrobial therapy on the part of physicians. This can be attributed both to failures of education in medical schools and hospitals, and the influence of specific product-related information from the pharmaceutical industry. Physicians probably get most of their information on antibiotics from pharmaceutical companies, and this needs to be balanced by impartial guidance from independent microbiologists and infectious diseases physicians. Educational programmes aimed at improving usage have had variable results, but they can be successful, especially when they are combined with audit of antibiotic usage and feedback of results.

9. Numerous strategies have been proposed to improve antibiotic usage in hospitals. Most authorities recommend the publication of a formulary that limits the agents available for prescription from the hospital pharmacy, and this may be supplemented by specific written antibiotic guidelines or a hospital antibiotic policy. Separate policies may be needed for specialised units such as intensive care units or the haematological oncology service. Since antibiotic policies imply some loss of individual clinical freedom for the benefit of the hospital as a whole, they should be overseen by a hospital committee consisting of senior physicians, surgeons, microbiologists and pharmacists, and having the power to implement their decisions. The committee needs to meet regularly to revise and update the hospital policy that will change with changing circumstances.

10. After the reduction of unnecessary antibiotic usage, the control of resistant bacteria in hospitals depends on the implementation of rational programmes of infection control. As hospital pathogens become increasingly antibiotic resistant, prevention of infection and spread assumes ever greater importance. Infection control programmes are the same for both sensitive and resistant bacteria.

11. Patients who have infection or asymptomatic colonisation with antibiotic-resistant bacteria should be isolated and staff should pay strict attention to handwashing. Urinary catheterisation is associated with considerable risk of cross infection with resistant organisms, and staff should follow hospital policies for urinary catheter care. Similarly, policies for the insertion, management and removal of vascular catheters should be followed to reduce infection with resistant skin bacteria.

12. Gram-negative opportunistic pathogens are often inherently antibiotic and disinfectant resistant and may survive and proliferate in nutritionally poor environments. Thus they contaminate diluted disinfectants and medications, and wet environmental sites such as ventilator, humidifiers, water systems, sinks and drains. Programmes should be instituted to ensure clean and safe disinfectants; reliable methods to decontaminate hospital equipment and environment sites should be established; and single-usage or individual medications, creams, jellies and ointments should be employed.

REFERENCES

1. Report of a combined working party of the Hospital Infection Society and the British Society for Antimicrobial Chemotherapy. Revised Guidelines for the control of epidemic methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* (1990) 16: 351-377.
2. Patterson JE and Zervos MJ High-level gentamicin resistance in *Enterococcus*: microbiology genetic basis and epidemiology. *Rev Infect Dis* (1990) 12: 644-652.
3. Allen KD Penicillin-resistant pneumococci. *J Hosp Infect* (1991) 17: 31-43.
4. Recommendations for preventing the spread of vancomycin resistance. *Infection Control Hospital Epidemiology* (1995) 16: 105-113.

Memorandum by Dr Brian Watt, Edinburgh Royal Infirmary

I am writing in response to the Call for Evidence with the following comments:

1. In Scotland, surveillance of bacterial infections is performed under the auspices of the Scottish Centre for Infection and Environmental Health (SCIEH), in collaboration with local bacteriology laboratories, National Reference Laboratories and Consultants in Public Health Medicine and the Scottish Office (Electronic links between these participants are to be put in place, as one of the recommendations of the Pennington Report). There is no PHLS in Scotland.

2. Data on bacterial resistance may be collected for some pathogens (eg *M. tuberculosis*, MRSA) but is not collected systematically for all pathogens.

3. Multi-drug resistant tuberculosis (MDRTB) is found in small numbers of patients in Scotland (1 per cent in 1996), but there is as yet no discernible trend, numbers varying from 0 to 1 per cent over the past five years.

Although these patients pose therapeutic challenges, they have not been associated with outbreaks of MDRTB.

4. Continuing close surveillance of tuberculosis is essential, including sensitivity testing of all strains. New molecular methods will allow for rapid detection of resistant strains, but will be expensive, and will have to be applied to most if not all strains. Streaming of strains according to "index of suspicion of MDRTB" would have failed to detect 2 out of 3 cases in 1996.

5. Prevention of the causes of MDRTB is extremely important. Anecdotal evidence suggests that not all patients are treated according to established guidelines. Treatment of tuberculosis needs to be audited on a national basis to determine the degree of compliance with guidelines.

6. The new guidelines on MDRTB and HIV-associated tuberculosis need to be published as soon as possible and their recommendations implemented in full.

7. Control of Infection advice for tuberculosis is readily available in Scotland, but policies need to be more formalised.

8. The risks of tuberculosis associated with long-haul flights are considerable, and contact tracing is hampered, often, by difficulties in obtaining passenger manifests from the airlines.

9. A workshop on the problems outlined, in paragraph 8, would help to formulate a clear approach—but there may have to be Government discussions with the travel industry as well.

10. As far as other resistant bacterial infections are concerned, the ones that cause most concern as sources of hospital-acquired infections are MRSA and VRE (vancomycin-resistant enterococci). Both of these are easily spread and difficult to treat, and the recent reports of vancomycin resistance in MRSA are worrying (vancomycin or its analogues are often the only agents available for the treatment of systemic MRSA infection).

11. Media coverage of antibiotic-resistance is often ill-informed and alarmist. More public information, presented in a straightforward but informative way, would be helpful.

12. The development of antimicrobial drug resistance can be slowed/minimised by proper guidelines on antibiotic prescribing, and responsible marketing of new antimicrobial agents, especially those which should be used as “reserve” drugs.

I submit these comments in two capacities:

1. Director, Scottish Mycobacteria Reference Laboratory.

2. As a Consultant Microbiologist who is Chairman of the Royal Infirmary of Edinburgh NHS Trust Control of Infection Committee.

B Watt, MD, FRCPath, FRCPEdin, FIBiol, CBiol.

19 August 1997

Memorandum by Zeneca Pharmaceuticals

1. Zeneca Pharmaceuticals submission is limited to areas in which our research is current and has been copied to the ABPI.

2. Resistance to anti-infective agents is a complex problem of increasing significance in the UK and internationally where it is no longer confined to the hospital environment. The extent of the problem remains to be quantified accurately and in the process of defining the magnitude of the problem in the UK it is important that the data are generated and collected in a manner which allows it to be integrated with similar studies which are being conducted by major authorities such as the WHO and the CDC in the USA. The WHO is thought to have computer software (WHONet) for this purpose which has been developed in conjunction with CDC personnel.

3. The problem of bacterial resistance to therapy has indeed reached a new level of significance with the realisation that there are pathogenic bacteria for which no adequate therapy is available; the current topical example is *Enterococcus* species. Perhaps as significant is the fact that antibiotics such as cephalosporins, which are the backbone of hospital empirical therapy are already, or are becoming, ineffective against an increasing number of bacterial species. Similarly, important anti-fungal agents are failing to treat fungi which have developed resistance or have emerged in institutions in which the use of these agents is extensive. This is a significant issue for late-stage AIDS patients and for the increasing numbers of otherwise immunosuppressed patients.

4. The fact that anti-microbial resistance is invariably at its greatest in hospital intensive care units, where anti-infective therapy is most aggressive, implicates concentrated use of agents as an indicator of the development of resistance. However, cost constraints frequently result in inappropriate antibiotic use with ensuing prolongation of hospital stay. It would be wrong to think of resistance as being limited only to these specialised hospital units; it can occur and spread alarmingly in nursing homes and is also seen in the community. Consequently, a process of education is imperative to improve this situation.

5. An understanding of the significance of new resistance mechanisms, some of which may be shared by unrelated chemical classes of antibacterial agents, is important. Some observations are indeed of great significance and warrant detailed studies whereas others require to be put into perspective. This latter point is exemplified but the concerns about pneumococcal infections which, based on laboratory criteria, are highly resistant to established therapies but typically can be treated by elevated doses of penicillin. Standardised laboratory methodology is required also; currently, the spread of transferable resistance which confers

resistance to cephalosporins frequently is undetected because of the use of inappropriate methodology. Once again, education is required.

6. The UK government has the opportunity to advance the scientific understanding of the issue by supporting and funding a surveillance study and surrounding research which is being planned jointly by the UK Public Health Laboratory Service and the British Society of Antimicrobial Chemotherapy (BSAC). Draft EU legislation proposals to require that surveillance of emergence of resistance to newly registered anti-infectives will be mandatory and will be the responsibility of the pharmaceutical company are misplaced. They should not be the sole responsibility of the pharmaceutical industry.

7. The pharmaceutical industry has consistently developed new anti-infective agents during the past 50 or so years which have provided a breathing space before further issues of resistance have emerged. Regulatory requirements have become increasingly demanding and costs have escalated causing many companies to question the value to their business of the development of new anti-infective agents. Further, at an FDA meeting in 1996, the suggestion that new agents should be registered only for treating resistant bacteria was made. Regulations, costs, highly segmented markets and constraints on use are all contra-indications to the devotion of efforts to anti-infective research programmes.

8. With Zeneca Pharmaceuticals, our new anti-infective discovery programmes are based on genomic information which seeks to identify targets which are not shared by microbes and man and which would ultimately be effective therapies for bacterial or fungal infections which are resistant to many current agents. This represents a significant investment which includes external collaborations and will take many years to produce new drugs. In support of our marketed anti-infectives, we recently conducted a 56-centre surveillance programme in the UK and continue with studies in Europe and the US. We consider it important to interact with established Societies and authorities and to that end we are represented on the BSAC/PHLS surveillance management team, are interacting with WHO with the wish to use their WHONet software and also with CDC who we are funding to conduct two US studies.

9. Zeneca Pharmaceutical welcomes the Committee initiative on microbial resistance and wishes to offer our experience to support your endeavours should you deem this appropriate.

23 September 1997

Supplementary memorandum by Professor S G B Amyes

Last year I submitted evidence to the House of Lords Select Committee on the main problems I saw of Antibiotic Resistance. I have spoken with colleagues and, as Head of Department of the largest Medical Microbiology Department in a Scottish university, comment as follows on the state of Medical Microbiology:

Research into the problems and causes of antibiotic resistance is, and should be, multi-disciplinary. However, the most important and informed contributions will be from medical microbiologists. They are the only group with sufficient experience and knowledge to tackle the problem. The medical faculties of many universities are either downsizing their microbiology departments, subsuming them into divisions of pathological sciences, or replacing bacteriologists with virologists.

This has created a shortage of medical microbiologists suitably trained in bacterial research. In the University of Dundee, the Medical Microbiology Department has been downsized and, unless there is imminent recruitment of bacteriologists to the staff, the discipline will soon disappear. In the University of Glasgow, the academic department is divided between two sites (disadvantageous for constructive research) and downsizing by the University has left few bacteriologists.

Neither Dundee nor Glasgow are in a position to train large numbers of medical microbiologists, either undergraduates or science post-graduates. The University of Aberdeen has a Medical Microbiology Department that is larger than either Dundee or Glasgow. This department has a reasonable complement of medical microbiologists, with some specialising in bacteriology.

My own department is the largest Medical Microbiology Department in Scotland and perhaps in Britain. Its size should not suggest that the department is without problems, rather that it has maintained this position by the stubborn determination of its staff to preserve the subject in the face of almost overwhelming outside threats:

1. Medical microbiology is perceived by many in university medical faculties as an unnecessary subject. Medical microbiology vacancies are often unfilled or the money redirected to more "topical" disciplines. More disturbingly, bacteriologists are replaced by virologists because it is felt that they are likely to raise more money in grants.
2. Grant-awarding bodies, particularly the MRC, have been unfavourable towards grant applications on bacteriological subjects, especially those on antibiotic resistance. I have noticed an interesting turnaround in some grant-awarding bodies since the subject of antibiotic resistance became prominent in the public perception. Unfortunately other grant-awarding bodies have not followed this trend. This has forced many researchers to go to the pharmaceutical industry for funding. This has two major disadvantages. Firstly, it might not be perceived as unbiased and it is true that some pharmaceutical companies may try and control the direction of the study. Secondly, the universities and the Research Assessment

Exercise (RAE) perceives this source of money as less “virtuous” than money from the research councils. However, pharmaceutical companies are very accountable and can be very discriminatory in their distribution of funds, their research has to satisfy their shareholders. The MRC has set up a system of co-operative grant funding requiring applications from consortia comprising current grant holders. This is unfortunately prejudicial against bacteriologists and research into antibiotic resistance.

3. The Research Assessments Exercise has been disastrous for almost all medical microbiology departments that have a clinical diagnostic commitment. Some of these departments, notably in Scotland, have academic staff who have university contracts but are fully funded by their teaching hospital trusts. These staff have honorary consultant contracts and, in essence, are full-time clinical staff who do some teaching. They have little time for research and what they can fit into their very busy schedules is rarely cutting-edge. When the departments are assessed in research, their universities often insist that 95 per cent of staff are included. The clinical diagnostic staff considerably weaken any assessment of a Clinical Laboratory Science department and the RAE should recognise and accept this fact.
4. There is a move to separate diagnostic laboratories from academic departments. This is likely to considerably weaken both. Research in academic departments requires ready access to clinical specimens and the management of clinical specimens benefits greatly from close academic input.

The academic dilemma about medical microbiology is that industry is hungry for well-qualified graduates, particularly in bacteriology. It is also particularly popular with the students. In our department, we have 50 students in our honours year, this is the second largest honours school in either biological science or medicine. We also have 38 PhD students, more than any other medical discipline. The students are extremely keen to study the subject, but many universities are progressively denying the opportunity. I should mention that very few of these PhD students are funded by the Research Councils or by the University. More than two-thirds are supported by the efforts of the staff independently raising the funds for the studentships.

If medical microbiology is to survive as a subject, then it must enjoy much greater funding, both from central government and from the universities. The problems of antibiotic resistance will not be solved without the continuing input of well-trained medical microbiologists with well developed skills in bacteriology.

11 February 1998

Memorandum by the British Association for Chemical Specialities

The British Association for Chemical Specialities (BACS) is a trade association of some 170 member companies. These include most producers of biocidal products for hospital, institutional, domestic and industrial use—ranging from disinfectants, antiseptics, bleaches and hygienic cleaners, to industrial biocides and preservatives.

BACS members share concern about the problems of micro-organisms developing resistance to antibiotics, and the potential consequences for public health, clinical medicine and surgery, in terms of compromised ability to treat bacterial infections.

Although the major causes of antibiotic resistance are well known, BACS has become aware that some evidence presented to your Committee has suggested links between use of, and resistance to, certain biocidal products and the development of resistance to antibiotics. BACS believes it is important to understand any such links, particularly any instances of cause and effect, not least because preventing infection—in which biocidal products play a key role—becomes more important if ability to treat infection is reduced.

TECHNICAL COMMENTS

Biocidal products use many different types and combinations of active ingredients, which act by a very diverse range of mechanisms. Some interfere with processes inside microbial cells; others affect processes or sites around the cell membrane, while some biocides at higher concentrations can chemically degrade the cells. Whereas antibiotics act against specific sites or physiological functions, most biocides act more generally against multiple sites or processes.

Different bacteria naturally have different susceptibilities to individual biocides and antibiotics according to their mode of action. Increased resistance to an antibiotic sufficient to compromise its usefulness in clinical practice (“high-level” resistance) usually stems from genetic alterations (by mutation or plasmid transfer) which cause substantial and specific changes in structural proteins or enzymes.

As with antibiotics, development of resistance to biocides stems largely from misuse—eg selection effects when inadequate concentrations, temperatures and/or contact times create sub-lethal conditions. In contrast, increased resistance to biocides is usually of a much lower order—adaptive changes rather than true resistance. These usually involve general mechanisms such as changes in the outer layers of the cell to deny the biocide access, or “efflux pumps” which expel biocide from the cell. Such effects are also reversible and, importantly, can equally well result from natural stresses.

Only for a few biocides has a stable increase in resistance, plasmid or chromosome mediated, currently been seen, eg that encoded by *qac* (for one species (*Staph. aureus*)) or *mar* genes which control biocide efflux from the cell. In both cases, however, these increases—typically up to 10-fold in minimum inhibitory concentration (MIC) for laboratory strains—are small in relation to the concentrations used in practice. They do not necessarily translate to “wild” strains, nor mean that the product becomes ineffective.

Though some links between mechanisms of resistance to biocides and antibiotics have been suggested, their implications, if any, are entirely unclear. For example, Levy¹ has shown that exposure of *E. coli* to low-levels of a biocide (pine-oil) in the laboratory can select mutant strains which naturally express proteins (*mar*). These accelerate efflux pumps, increasing MICs (2-10 fold) for certain antibiotics as well as pine-oil.

Such low-level changes are of little concern *per se*, though the suggestion is made that they may somehow favour the acquisition of additional resistance by plasmid-transfer. Miller and Sulavik², however, review evidence that induction of efflux mechanisms which resist antibiotics is not confined to biocides: other common environmental stresses, ranging from substances like weak acids, ethanol and salt to physical stresses such as starvation, osmotic and temperature stress, produce a similar response. They also suggest these mechanisms originated as defences for bacteria to naturally-occurring toxins, into which class both the active ingredients of pine-oil and several antibiotics would fall.

Resistance involving specific plasmids that also affect antibiotic sensitivity has been seen for a few specific biocides eg some metal salts and cationics. But although in some cases resistance to antibiotics and biocides run parallel, there are others where antibiotic-resistant organisms are more sensitive to some biocides.

While the implications of such links are unclear, the patterns of development of resistance to antibiotics in the field do not correlate with patterns of biocide use—indicating there is no major causative link. Since they first came into use over a century ago, biocides have been used in both homes and hospitals, increasingly in the former, and more selectively in the latter. Yet strains of bacteria resistant to antibiotics are clustered in hospitals, not in homes.

Biocides are used to eradicate methicillin-resistant *Staphylococcus aureus* (MRSA) from the skin, and for environmental cleaning during MRSA and vancomycin-resistant *enterococci* (VRE) outbreaks since some of these highly antibiotic-resistant organisms remain very sensitive to these biocides. This is despite the observation that *qac* genes in MRSA act to *increase* its resistance to certain biocides.

CONCLUSIONS

The apparent links between some mechanisms of resistance to biocides and antibiotics are complex and there is no unifying hypothesis on which to base conclusions about possible adverse or beneficial implications. However, the history and pattern of use of biocides does not correlate with emergence of antibiotic resistance, which indicates there is no major causative link. Indeed, the major causes of antibiotic resistance are well known, and if biocides do have some contributory role, the evidence indicates this is likely to be minor. At present, there is no evidence of any clinical significance.

Moreover, it seems the general mechanisms involved, such as efflux pumps, may well be a normal response to any kind of stress, including substances well beyond the ranks of recognised biocides and antibiotics, as well as physical stresses. Indeed, what are seen as “increased” levels of resistance on stressing laboratory organisms accustomed to ideal conditions may well be entirely normal for “real world” organisms that are constantly subject to stress.

Should antibiotic resistance continue to reduce our ability to treat certain infections, then preventing infection, in which biocides have for more than a century played a vital part, becomes of even greater importance. Understanding any links between biocide and antibiotic resistance, including any element of cause and effect, is thus important to inform the continued responsible use and prudent future development of the biocidal part of our armoury. BACS and its member companies are most willing to participate in any future considerations of this issue.

6 February 1998

Memorandum by the Chief Medical Officer, Northern Ireland

I am replying to your letter of 26 January about the Public Health Laboratory Service (PHLS)—type arrangements in Northern Ireland.

Historically there have been strong professional links between the Northern Ireland Public Health Laboratory (NI PHL) and the PHLS and these continue to be maintained in a positive and mutually beneficial manner—for example there is a reciprocal arrangement under which staff from the NI PHL have honorary consultant status at PHLS and vice versa, and many Specialist Registrars in Public Health Medicine from Northern Ireland have benefited from short-term attachments at the Communicable Disease Surveillance Centre (CDSC) as part of their training. In addition there are good collaborations in:

¹Levy, SB et al (1997) Antimicrob. Agents Chemother. **41** (12) 2770-2772

²Miller, PF and Sulavik MC (1996) Mol. Microbiol. **21**, 441-448

- tuberculosis—Northern Ireland and Scotland are integral parts of MYCOBNET, the surveillance system for drug resistance in *Mycobacterium tuberculosis*; and
- HIV/AIDS—figures are compiled on a UK basis—a process which involves collaboration between Northern Ireland, PHLS and Scotland—and are then published by PHLS.

The NI PHL is located on the Belfast City Hospital site within the Eastern Health and Social Services Board area and is managerially part of the integrated laboratory service of the Royal Hospitals and Belfast City Hospital Trusts. The NI PHL provides a regional public health microbiology service for Northern Ireland, although clinical specimens related to outbreaks in other Health and Social Services Board areas are examined in the nearest hospital laboratory.

The services currently provided by the NI PHL cover food and environmental microbiology, support for outbreak investigation, supply of vaccines and immunoglobulins, advice on aspects of communicable disease control, teaching and training, research and reference work. I am mindful that you wish to have as succinct a response as possible for the Committee and so I am moving some of the detail to annexes—further information on the services carried out by NI PHL is therefore to be found in Annex A.

A virology service for all Northern Ireland is provided by the Regional Virus Laboratory which is based on the Royal Hospitals Trust site.

The NI PHL along with the other laboratories in Northern Ireland report a comprehensive list of microbiological data to the Department of Health and Social Services (DHSS). This list is largely the same as that used in England and Wales by the PHLS CDSC. These laboratory data and notifiable disease tables are published by DHSS in a monthly report Communicable Disease, Northern Ireland.

In 1997 on foot of the tragic outbreak of E Coli 0157 in Central Scotland, I commissioned a wide ranging review of the arrangements for communicable disease control in Northern Ireland. One of the key recommendations of the report on the review was that DHSS should establish a Regional Communicable Disease Epidemiology Unit, independent of but reporting to DHSS, to assist it in fulfilling its role in the control of communicable diseases. Additional information on the recommended remit for the Unit is set out in Annex B.

DHSS has initiated action to implement this recommendation and will discuss with PHLS how best to take the matter forward with a view to strengthening links with PHLS. The Department has given this recommendation a high priority and intends moving urgently towards its implementation. The report also recommends that DHSS convene a small working group, which should include an external consultant from PHLS, to draw up detailed specifications for the core activities, management, funding and accountability of the NI PHL.

In conclusion, the Department is committed to ensuring that the standard of PHLS-type services provided in Northern Ireland is at least as high as those in the rest of the UK while taking into account the Province's local arrangements for the provision of health services, our separate legislative base and the particular issues raised as a result of our land border with the Republic of Ireland. We feel that the arrangements which are in place, or are about to be implemented, provide the best way of ensuring that these aims are met. The Department will of course continue to liaise closely with PHLS and the Scottish Centre for Infection and Environmental Health in sustaining and improving the standard of these services in Northern Ireland.

10 February 1998

Annex A

NI PHL

Food and environmental microbiology is carried out for the whole province.

Support for outbreak investigation, including examination of clinical specimens and food samples, is regional but provided largely to the Eastern Board, partly reflecting the geographic location of the laboratory but also the concentration of population in this area.

Vaccines and immunoglobulins are supplied for pre- and post-exposure prophylaxis eg rabies vaccine and Varicella Zoster immunoglobulin.

Advice is provided to DHSS and Departments of Public Health Medicine on aspects of control of communicable disease and to EHOs on sampling.

Teaching and training is provided for a range of professional groups. The Laboratory is recognised for specialist registrar training in microbiology.

Research activities include participation in national programmes relating to the microbiological safety of food. Campylobacter research has been a particular focus.

Some reference facilities are provided, including extensive serotyping facilities for salmonella identification, mycobacteria identification and sensitivity testing, legionella serology and culture (both clinical and environmental), and leptospira serology.

REGIONAL COMMUNICABLE DISEASE EPIDEMIOLOGY UNIT

The report on the review of the arrangements for communicable disease control in Northern Ireland recommended that the remit of the Regional Epidemiology Unit should include—

Epidemiological surveillance:

- Laboratory confirmed infections, in particular foodborne infections;
- Notifiable diseases;
- Sexually transmitted diseases including HIV and AIDS;
- Hospital acquired infection;
- General practice sentinel surveillance eg for influenza;
- Sero-surveillance;
- Drug resistant organisms including MRSA; and
- Emerging pathogens.

Expert advice and support for the investigation of outbreaks.

Advice and guidance on communicable disease control promoting a coherent and consistent policy across the province.

Liaison with similar units in the rest of the UK, the Republic of Ireland and other European Union countries.

Education, training and audit.

Research & development.

Regular evaluation of the surveillance systems using a standard protocol such as that published by the Centers for Disease Control.

In addition the report recommended that the Unit should establish active links with the CsCDC, Consultant Microbiologists, Infectious Disease Physicians, Environmental Health Officers, Veterinary Service and other agencies as appropriate.

Memorandum by Professor George E Griffin, St George's Hospital Medical School

BACKGROUND

Antibiotics are highly effective agents and since their introduction have revolutionised Clinical Medicine. Many chemical groups of antibiotics are now in clinical usage. The development of these agents follows a basically similar pathway involving the isolation and characterisation of antimicrobial agents produced synthetically or by micro-organisms. Such agents after chemical characterisation are then subject to detailed microbiological assessment and enter toxicological studies, first in animals and then in humans in the United Kingdom. Human studies are initially controlled by licence from the Medicine Control Agency (MCA) and local ethical committees. Following human clinical studies, a licence for clinical indication and usage of a particular antibiotic is given by the MCA and the drug is marketed. Such development schemes for antibiotics are financed by pharmaceutical companies. The development process from isolation of novel compounds to the market involves many millions of pounds for an individual agent and takes around a decade.

CLINICAL RESEARCH IN ANTIBIOTIC USE

Despite the widespread use of antibiotics in human clinical conditions, we are still ignorant of many important facts, both of a basic clinical therapeutic and microbiological nature. For example clinical practice in the treatment of severe infections differs considerably between countries. This is particularly true for management of otitis media, bacterial endocarditis and urinary tract infection, in which the duration of antibiotic treatment varies greatly. In the microbiological arena, the emergence of resistance during standard courses of antibiotic treatment lasting for one to six weeks in normal and immunocompromised patients is not documented or understood. In addition, in immunocompromised individuals it is common to give "lifelong" antibiotic prophylaxis against specific pathogens and we do not know the effects of such chronic agents used in individual patients on emergence of antimicrobial resistance.

FUNDING FOR CLINICAL RESEARCH ON ANTIBIOTIC USE

The emergence of resistance to antibiotics has proved to be a great stimulus for detailed molecular analysis of basic mechanisms, which has been very fruitful and important. In contrast, research in the clinical use of antibiotics and application of basic microbiological knowledge to clinically based research has proceeded at a very slow rate. Funding for research is becoming increasingly difficult to obtain in the United Kingdom and

avenues to finance and facilitate clinically based research on antibiotic usage are urgently needed. Such avenues might include specific initiatives funded by research councils and charities and NHS Research and Development.

Memorandum by Dr H F Kennedy and Dr J R Michie, Royal Hospital for Sick Children

THE EMERGENCE OF GLYCOPEPTIDE RESISTANT GRAM POSITIVE BACTERIA IN THE ROYAL HOSPITAL FOR SICK CHILDREN, GLASGOW

INTRODUCTION

1. The Royal Hospital for Sick Children (RHSC), Glasgow is a 320 bed teaching hospital. In 1995 the first glycopeptide resistant Gram positive bacteria were cultured from clinical specimens from patients in the Haematology/Oncology Unit.

2. The glycopeptide antibiotic, vancomycin is used extensively in the high dependency units of RHSC, while teicoplanin is used to a much lesser extent. Both of these antibiotics are important in the control of serious infections caused by Gram positive bacteria, including those caused by methicillin resistant *Staphylococcus aureus*, therefore the development of resistance to glycopeptides is a cause of great concern.

3. This report describes the emergence of glycopeptide resistant Gram positive bacteria in RHSC and discusses the associated clinical implications.

RESULTS AND DISCUSSION

4. Although the sample sizes are small, the data in Table 1 illustrate the incidence of and suggest an increasing trend in cases of colonisation/infection by glycopeptide resistant Gram positive bacteria over a period of 29 months. Colonisation of the gastrointestinal tract (as demonstrated by our earlier cases) may precede infection by these organisms¹.

5. *Enterococcus gallinarum* and *Enterococcus casseliflavus* are intrinsically resistant to low levels of vancomycin but susceptible to teicoplanin. *Leuconostoc* species, *Pediococcus* species and *Lactobacillus* species are intrinsically resistant (at high levels) to both glycopeptide antibiotics.

6. *Enterococcus* species and *Lactobacillus* species form part of the normal gastrointestinal bacterial flora of man. *Leuconostoc* and *Pediococcus* species are commonly found on plants and in vegetables and dairy products. Little is known regarding the route or mechanism by which these organisms colonise or cause infection. Bacteraemia caused by these opportunistic pathogens is rare but can cause considerable morbidity in immunocompromised cancer patients², while mortality due to infection by glycopeptide resistant *E faecalis* and *E faecium* has now occurred in several centres^{1,3}.

7. Glycopeptide resistance in *E faecalis* and *E faecium* is inducible and has been transferred experimentally to *S aureus*, raising concerns that a similar situation may eventually arise *in vivo*. All isolates of glycopeptide resistant *E faecalis* and *E faecium* from our patients were resistant to high levels of both vancomycin and teicoplanin (ie exhibited the *Van A* phenotype).

8. The majority of patients (75 per cent) colonised or infected by Gram positive glycopeptide resistant bacteria in RHSC were being treated for malignant disease (predominantly leukaemia), had been hospitalised for some time and had received prior antibiotic therapy which included vancomycin and the third generation cephalosporin, ceftazidime.

9. Although infection by intrinsically resistant organisms such as *Leuconostoc* species is less serious than that caused by glycopeptide resistant *E faecalis* and *E faecium*, our experience suggests that colonisation and infection by both groups of organisms emerged due to similar selection pressures. The use of vancomycin in individuals who already harbour low levels of these organisms in their gastrointestinal tract may cause overgrowth leading to infection. The alternative mechanism of infection by glycopeptide resistant *Enterococcus* species occurs as a result of transmission from a colonised or infected individual³. Cases 11 and 12 demonstrate an example of the latter scenario. The isolates of *E faecalis* from both patients were identified as the same strain using biochemical tests followed by PCR and pulsed field gel electrophoresis suggesting that an episode of cross infection had occurred.

ACTION

10. All patients who were either colonised or infected by glycopeptide resistant *E faecalis* or *E faecium* were isolated and infection control measures instigated. All bacteraemic patients responded to therapy with appropriate antibiotics. Fortunately all glycopeptide resistant organisms were sensitive to several β -lactam antibiotics including ampicillin and piperacillin, one of which was used in combination with the aminoglycoside antibiotic, amikacin. Other centres have reported strains of glycopeptide resistant *E faecalis* and *E faecium* which are also highly resistant to ampicillin and gentamicin, which renders such infections virtually untreatable¹. All faeces specimens from Haematology/Oncology patients in RHSC are now routinely screened for glycopeptide resistant enterococci.

OUTCOME AND CONCLUSIONS

11. At this moment in time, there are no cases of colonisation or infection by glycopeptide resistant Gram positive bacteria in patients in the Haematology/Oncology Unit at RHSC. Our experience of infection by such organisms, although somewhat limited, has served to introduce medical, nursing and laboratory staff to a new aspect of antimicrobial resistance. The emergence of glycopeptide resistant *E. faecalis* and *E. faecium* has necessitated the compilation of guidelines for prevention and control of nosocomial infections caused by these organisms. Hospital prescription of glycopeptide antibiotics is being reviewed and infection control guidelines specific to these organisms are being prepared. When laboratory tests detect the presence of these bacteria, prompt communication between Microbiology laboratory staff, the infection control nurse and ward staff is essential to limit the spread of antimicrobial resistance and limit the cost of expensive containment procedures.

ACKNOWLEDGEMENTS

Identification of all *Enterococcus* species by PCR and PFGE was provided by Dr M E Kaufmann and staff of the Epidemiological Typing Unit and all MIC results were provided by Dr A P Johnson and staff of the Antibiotic Reference Unit, Laboratory of Hospital Infection, PHLS Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT.

Table 1

FEATURES AND DATES OF ISOLATION OF GLYCOPEPTIDE RESISTANT BACTERIA, RHSC, 1995-97.

Date	Patient No.	Diagnosis	Isolate	Site	Vancomycin MIC (mg/l)	Teicoplanin MIC (mg/l)
24.05.95	1	ALL	<i>E. gallinarum</i>	Faeces	16(R)	1(S)
27.06.95	2	ALL	<i>E. faecium</i>	Faeces	> 32(R)	> 32(R)
15.12.95	3	ALL	<i>E. faecalis</i>	Faeces	> 32(R)	> 32(R)
01.01.96	4	NHL	<i>Pediococcus</i> spp	Blood	> 32(R)	> 32(R)
01.03.96	5	ALL	<i>E. casseliflavus</i>	Faeces	8(R)	2(S)
13.12.96	6	AML	<i>Leuconostoc</i> spp	Blood	> 32(R)	> 32(R)
05.02.97	7	Wilms Tumour	<i>Leuconostoc</i> spp	Blood	> 32(R)	> 32(R)
24.03.97	8	SCIDS	<i>E. faecalis</i>	L.L. Site	> 32(R)	> 32(R)
26.06.97	9	Pseudogut	<i>E. gallinarum</i>	Blood	16(R)	1(S)
05.08.97	10	Hydrocephalus	<i>E. gallinarum</i> , <i>L. rhamnosus</i>	Catheter-CSF	16(R) > 32(R)	1(S) > 32(R)
23.09.97	11	AML	<i>E. faecalis</i> *	Bone-Marrow, Faeces	> 32(R)	> 32(R)
26.09.97	12	ALL	<i>E. faecalis</i> *	Blood	> 32(R)	> 32(R)

ALL: Acute Lymphoblastic Leukaemia

NHL: Non-Hodgkins Lymphoma

AML: Acute Myeloid Leukaemia

SCIDS: Severe Combined Immune Deficiency Syndrome

L.L. site: Long-line site

MIC: Minimum Inhibitory Concentration

R: Resistant

S: Sensitive

*: Identical organism

REFERENCES

1. Noskin GA, Peterson LR, Warren JR. *Enterococcus faecium* and *Enterococcus faecalis* bacteremia: acquisition and outcome. Clin Infect Dis 1995; **20**: 296-301.
2. Golledge CL, Stingemore N, Aravena M, Joske D. Septicemia caused by vancomycin-resistant *Pedococcus acidilactici*. J Clin Microbiol 1990; **28**: 1678-1679.
3. Edmond MB, Ober JF, Weinbaum DL, Pfaller MA, Hwang T, Sanford MD, Wenzel RP. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. Clin Infect Dis 1995; **20**: 1126-1133.

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15 January 1998

Memorandum by the Ministry of Agriculture, Fisheries and Food

NOTE FROM THE MINISTER OF AGRICULTURE, FISHERIES AND FOOD IN RESPONSE TO QUESTIONS RAISED BY THE COMMITTEE IN RESPECT OF A SUBMISSION FROM DR GERALD C COLES, MA, PHD, CBIOL, FIBIOL, ON RESISTANCE TO ANTIMICROBIAL AGENTS.

1. Is it the case that MAFF ended compulsory dipping of sheep and notification of sheep scab in 1992? Why?

The introduction of organochlorine dips in 1947, together with infested area controls led to eradication of the sheep scab in 1952. Unfortunately, it was reintroduced in 1972.

Attempts to control and eradicate the disease over the following 20 years failed despite notification, compulsory treatment of flocks found to have the disease and national dipping. It became apparent that notifiable disease status and the existing legislation, while controlling it, was unlikely to eradicate the disease. Sheep scab was deregulated in 1992 and although still listed as Notifiable to a police constable in the Animal Health Act 1981, no further controls were applied.

However, since 1992 the disease has spread despite the availability of effective treatments. The mounting concern expressed by the sheep farming community led to the previous Government re-examining the issue of control. Two areas of specific concern were identified which were the irresponsible owner/dealer and the difficulty of co-ordinating treatment of common grazings.

The Government of the day concluded that a policy of eradication was unworkable but, as farmers were responsible for the health and welfare of their sheep, policy should be to help the industry's own efforts to control scab. This policy led to the introduction of the current Sheep Scab Order 1997. This Order addresses the areas of concern by making it an offence to move sheep visibly affected with scab and by requiring their treatment. It also gives local authorities powers to clear common land when visibly affected sheep are present on it.

2. Does MAFF consider that the UK sheep flock now has a problem with resistant sheep scab mites? How does MAFF propose to address it?

MAFF is aware of reports on the limited existence of sheep scab mites in the UK flock which are resistant to either pyrethroid or organophosphate classes of treatment compounds. However there is no evidence of such mites having a resistance to both pyrethroids and organophosphates. There are no recorded cases of resistance to ivermectin, the third class of treatment compound, in sheep scab mites anywhere in the world.

We consider therefore that there are effective treatments currently available against sheep scab in the UK flock.

The potential problem of the further development of acaricide resistance in sheep scab mites is nevertheless recognised and MAFF is funding research into the factors which are involved, together with surveillance methodology, and possible alternatives in sheep scab control.

3. Is it the case that MAFF's research programme for 1996-2000 covers resistance to pesticides but not resistance to parasiticides? Why?

It is not the case that MAFF's research programme for 1996-2000 does not cover resistance to parasiticides.

MAFF has funded 10 research projects related to resistance to parasiticides between 1995-96 and 1997-98 to a value of about £2.5 million. Several of the current projects, with total projected costs of about £1.1

million, continue into future years (see attached table), while others are being considered for funding. The full programme of research up until 2000 has not yet been finalised and additional work on parasiticide resistance will be considered against other policy requirements for research.

These projects are part of the research programme on Endemic Diseases which cost about £19 million between 1995–96 and 1997–98. This research programme covers non-statutory animal diseases that are not considered to be zoonoses (infections of animals that can be transmitted to man).

The MAFF programme consists of applied strategic and applied specific research. The applied strategic research is directed to understanding more about the host-parasite relationship with the long term aim of elucidating novel mechanisms by which parasitic diseases can be controlled. The applied specific research is aimed at applying research to develop novel disease control methods, to developing methods for detecting resistance and to developing computer models to optimise strategies for controlling parasitic diseases to maximise the effectiveness of current control methods and minimise the development of parasiticide resistance. Thus the long term and shorter term aims of the programme have relevance to the problem of resistance development to parasiticides.

In addition to MAFF there are several other Government sponsors of parasite research, including DANI, BBSRC and particularly SOAEFD. The programmes of the funders are co-ordinated through a Funders Group in order to ensure efficient use of funds and to prevent unnecessary duplication. The research programmes are complementary; for example SOAEFD funds research aimed at genetic approaches to parasite control as part of a large strategic research programme on ruminant parasites. Overall SOAEFD takes the lead research role for most diseases of sheep.

OTHER COMMENTS

Sheep Scab Order 1997

At paragraph 6.1.3 of the submission from Dr G C Coles, he raises two major problems regarding the effectiveness of the Sheep Scab Order 1997. These relate to the diagnosis of sub clinical scab and the rapid sensitive tests to detect resistance to treatment.

The objective of the Sheep Scab Order is not to eradicate the sheep scab mite but to facilitate the control of clinical disease by sheep farmers. The Order includes powers which penalise those who fail to treat animals with visible sheep scab. Because the Order is only concerned with cases of scab where the signs should be apparent to the owner of an affected animal, the difficulties of diagnosis of sub clinical scab will not detract from its effectiveness. Greater control over clinical scab will reduce the spread of the sheep scab mite.

Difficulty in determining resistance to approved veterinary treatments is not a factor that the Sheep Scab Order can address. The Order requires the treatment of visible sheep scab. Any farmer who experiences problems with the effectiveness of a particular treatment should report the matter to the Veterinary Medicines Directorate and consult his veterinary surgeon for advice on alternative means of control.

Helminths

Dr Coles' comments relating to human helminths are not strictly relevant to the UK as the majority of infections are tropical (with the exception of pinworms) and only rarely reported in this country. Research into drug resistance to veterinary helminths has been ongoing for nearly two decades in the UK.

With sheep and goat nematodes the world-wide situation is certainly of concern as multiple resistance has been reported in several species in a number of countries throughout the southern hemisphere. In the temperate latitudes of the northern hemisphere where the epidemiology of gastro-intestinal nematodes is different, the situation does not appear to be as serious but nevertheless merits some degree of concern. Benzimidazole resistant nematodes are now often reported in the UK, particularly in the south of England, but clinical cases associated with their presence remain uncommon.

Reference to up to 20 per cent of flocks in the south-east having the beginnings of levamisole resistance (paragraph 5.1.3) is not correct. This refers to current research at the Central Veterinary Laboratory of the Veterinary Laboratories Agency. Of 100 samples submitted for in-vitro testing, 20 showed evidence of resistance genotypes being present. However, resistance has not been confirmed and certainly does not suggest a flock incidence at this level.

It is thought that in the UK resistance to drugs for use against fluke is theoretically likely to be slow to develop. The resistance to closantel in the UK fluke isolates (paragraph 5.5) was in the opinion of many scientists in the field, unsubstantiated. The two strains showed a tolerance at very low therapeutic levels well below the recommended dose rate of 10 mg/kg used in the UK.

Protozoa

Coccidiosis resistance, has been and continues to be a cause for concern to the poultry industry. A succession of anticoccidials have been produced and have rapidly been lost due to resistance developing. The introduction of new anticoccidials has declined rapidly and re-cycled older products are again failing. The introduction of a live attenuated vaccine offers some hope but there are many questions remaining unanswered. A review on the subject is in preparation and should be completed by April 1998.

MAFF RESEARCH RELATED TO RESISTANCE TO PARASITES

<i>Project Code</i>	<i>Title</i>	<i>Contractor</i>	<i>Start Date</i>	<i>End Date</i>	<i>95-96 Costs</i>	<i>96-97 Costs</i>	<i>97-98 Anticipated Costs</i>	<i>98-99 Proposed Costs</i>	<i>99-00 Proposed Costs</i>
OD0506	Immunological Control of <i>Psoroptes ovis</i> Infections in Sheep	CVL	01/04/96	31/03/99		227,164	319,709	322,675	96,617
OD0507	The non-chemical control of sheep scab; a systems modelling approach combining ecology, ethology and epidemiology	LU	01/07/96	30/06/99		54,760	73,410	69,910	33,495
OD0508	Studies to determine the effect of counter-selection on reversion to anthelmintic susceptibility	CVL	01/04/94	31/03/97	20,554	124,316			
OD0511	Mechanisms of infection and immunity in coccidiosis	IAHCM	01/04/96	31/03/99		432,600	443,100	338,625	112,875
OD0521	The effect of fleece factors on the susceptibility of sheep to sheep blowfly (<i>Lucilia sericata</i>) attack	CVL	01/04/94	31/03/97	18,280	22,752			
OD0523	Mechanisms of immunity to coccidial infections	IAHCM	01/04/93	31/03/96	307,545				
OD0524	Early events in the pathogenesis of infection with <i>Eimeria</i> parasites	IAHCM	01/04/93	31/03/96	106,575				
OD0525	Studies on the pathogenesis and control of avian coccidiosis	CVL			73,556				
OD0527	Non-chemical methods for the control of Ectoparasites	CVL	01/04/95	31/03/98	46,530	55,298	40,158		
OD0528	An ELISA test for the sero-diagnosis of Sarcoptic mange in pigs	CVL	01/04/95	31/03/98	10,736	7,744	10,465		
OD0529	Delaying the onset of anthelmintic resistance—development of a model for parasitic gastroenteritis in sheep	CVL	01/04/97	31/03/00			68,492	78,423	79,654
TOTAL:					683,776	924,634	955,334	809,633	322,641
TOTAL MAFF SPEND ON ENDEMIC DISEASE RESEARCH*:					7,203,777	6,248,553	5,651,111		

CVL = Central Veterinary Laboratory; LU = Liverpool University; IAHCM = Institute for Animal Health, Compton

Memorandum by Dr H K F van Saene *et al*

A STEP BACK TO THE FUTURE; THE RESTORATION OF MICROBIAL ECOLOGY A PREREQUISITE FOR THE CONTROL OF ANTIMICROBIAL RESISTANCE IN SUSCEPTIBLE PATIENTS?

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INTRODUCTION

With the emergence of a methicillin-resistant *Staphylococcus aureus* [MRSA] also resistant to vancomycin in Japan¹, the prediction that ultimately many bacteria will become resistant to almost all antimicrobial agents may be on the way. The traditionalists see their warnings fulfilled. However, this "I-told-you-so" approach, was rarely accompanied by any new ideas of how to deal with the problem, and shows a lack of insight in the development of resistance. Some opinion leaders are devoid of perspective².

These forebodings on development of resistance illustrate the contrast between the genetic plasticity of bacteria and the intellectual rigidity of the attending physicians. Bacteria rapidly exploit random mutations gaining resistance that will help them to survive attack from new antibiotics. The physician's answer to the dynamic bacterial challenge seems only to rely upon manoeuvres of handwashing, barrier nursing, isolation, gowns, gloves³ and antibiotic formularies⁴. Two factors have accelerated the development of resistance. One is the accumulation of mutations over time so that, for a given micro-organism, entire classes of antibiotics have been rendered inactive⁵. The other is the failure to develop any new classes of antibiotics in recent years⁶.

However four critical observations have emerged recently implying that the actual situation is not as desperate as the traditionalists like to picture. [i] Resistant strains are often imported into the intensive care unit [ICU] by non-infected carriers, in addition to the development of resistance during the ICU stay⁷. [ii] Gut overgrowth is the primary event required for the expression of a resistant mutant⁸, transmission^{9,10} and superinfection¹¹. Once a particular PPM reaches the level of 10⁵ colony forming units/ml of saliva, the chance of isolating the identical micro-organism from the lower airways is 50 per cent¹¹. The higher the salivary and faecal concentrations of MRSA, the higher the spreading of it^{9,10}. In order to contain a resistant mutant, a bacterial population of a least 10⁶ is required⁸. [iii] Most newer antimicrobials promote a shift in flora and subsequent overgrowth due to their impact on the patient's gut ecology¹². [iv] ICUs that only use systemic antibiotics in combination with oral topical antibiotics as the most important component of selective decontamination of the digestive tract [SDD] in order to control overgrowth in long stay patients have not reported major problems of resistance, superinfections or outbreaks^{13,14}. These four observations that point to the gut as the site where resistant strains most often emerge, have consistently been ignored over the last two decades. Surveillance cultures of throat and rectum are required to detect these four phenomena. Routine surveillance of carriage of resistant micro-organisms is considered heretical because they may not predict infection in the individual patient and are costly. Besides "invisibility" of these phenomena, the lack of clearly defined terminology has contributed to the paucity of new ideas to fight the defiant bugs. After defining resistance in clinical terms, pathogenesis will be discussed followed by a comparison between the traditional and the new proposals for management of resistance.

WHAT DOES ANTIMICROBIAL RESISTANCE MEAN TO THE INTENSIVIST

The concept of clinical resistance is defined as the abnormal carriage of a resistant micro-organism by the ICU-patient¹⁵. A potentially pathogenic micro-organism [PPM] is considered to be clinically resistant to a particular antimicrobial if firstly the minimum inhibiting concentration (MIC)* for that colonising or infecting PPM is higher than the non-toxic blood concentration required to inhibit it following parenteral administration, and secondly if the minimum bactericidal concentration (MBC)** for that PPM carried in the oropharynx, stomach and gut is higher than the non-toxic concentration achieved after topical application. This patient-related definition of clinical resistance which we are advocating in preference to the conventional micro-organism-related definition of resistance, makes four fundamental assumptions. Firstly, the number of patients with a resistant micro-organism should be recorded for a proper documentation of the resistance problem in ICU. Secondly, for each patient the different sites that were infected by the micro-organism, eg lower airways, blood and wound should be registered for a resistance analysis. Importantly this second

*MIC—is the amount of antimicrobial in mg/L associated with inhibition of PPM *in-vitro*. *In-vivo* the assistance of leucocytes may be needed to obtain killing of the colonising or infecting PPM.

**MBC—is the amount of antimicrobial in mg/L needed to accomplish irreversible inhibition or killing of the PPM *in-vitro*.

criterion requires the exclusion of "copy" strains¹⁶. These are isolates with an identical sensitivity pattern isolated from the same site of the same patient at different times, as their inclusion may give a false impression of the size of the resistance problem. Thirdly, the micro-organisms have to be tested against the appropriate antimicrobials, eg, *P.aeruginosa* should not be tested for cefotaxime nor MRSA for ciprofloxacin. Fourthly, even when performing the appropriate test you have to distinguish between organisms which are naturally resistant to particular antimicrobials such as MRSA for flucloxacillin and *Proteus* spp to polymyxins, from organisms which become resistant having been previously sensitive, eg, *Klebsiella* and *Enterobacter* spp for cefotaxime, *Pseudomonas* spp for ciprofloxacin and *Acinetobacter* spp for carbapenems.

The intensivist faces three patterns of antimicrobial resistance in ICU: [i] aerobic Gram-negative bacilli [AGNB] multi-resistant to beta-lactams, aminoglycosides, beta-lactams combined with beta-lactamase inhibitors, fluoroquinolones and carbapenems such as *Klebsiella*, *Enterobacter*, *Acinetobacter* and *Pseudomonas* species; [ii] MRSA and [iii] vancomycin-resistant enterococci [VRE]. For an accurate record of emergence of resistance in ICU these are the target micro-organisms to be screened against the relevant antibiotics.

PATHOGENESIS OF EMERGENCE OF RESISTANT MICRO-ORGANISMS

Three elements have been identified as common factors in the problem of resistance in ICU, source, transmission and susceptible host¹⁷. In general, long-stay patients who carry the relevant strain form the major animate source. Carriage is often associated with overgrowth¹⁸ recognised as a risk factor for the presence of resistant mutant strains⁸, for the development of superinfections¹¹ and enhanced transmission¹⁹. Amongst the long-stay ICU patients, a subset of severely susceptible patients is almost always present. The interaction between the three elements is thought to be crucial in triggering an outbreak: the resistant strain from the source is transmitted amongst this subpopulation at high risk of infection to find minimally two ICU patients who will develop overgrowth followed by endogenous infection with the same strain.

SOURCES OF RESISTANT STRAINS

Inanimate objects alone are uncommon as sources of multi-resistant strains compared with animate objects in particular critically ill ICU-patients who require long-term [≥ 3 days] intensive care^{20,21}. Ventilation equipment, bags, urinometers, analysers have been described as common source outbreak of exogenous development. The micro-organisms commonly involved are multi-resistant *Acinetobacter*, *P.aeruginosa* and MRSA. They can be prevented by basic infection control measures directed to the external inanimate source. In general these outbreaks only last for a short period. Compared with the animate source, the long term ICU patients, this inanimate source is occasional and minimal. Patients both import resistant micro-organisms^{22,23} and may become carriers of resistant strains whilst in the ICU^{24,25}. Long stay patients who carry resistant micro-organisms are responsible for outbreaks that may last for years. Endemicity of resistance is related to the presence of one or more [even non-infected] carriers²⁶. AGNB multi-resistant to almost all classes of antibiotics, MRSA, the naturally resistant yeasts and VRE represent the main micro-organisms involved in the resistance problem in ICU. Staff or carers who in general enjoy a reasonably good standard of health are infrequently persistent carriers of multi-resistant strains²⁷. They readily clear the ICU strain following acquisition. There may be one exception in that carers with skin lesions such as eczema and psoriasis may harbour MRSA on their skin. In a classical outbreak, a primary endogenous pneumonia or septicaemia is often the reason for ICU-admission of the index case who—being inherently a carrier—imports the multi-resistant strain into the ICU¹⁷. Transmission via hands of carers is difficult to prevent completely²⁸. Secondary carriage and subsequent secondary endogenous infections occur in long-stay patients. Equipment does not escape contamination following transmission, closing the vicious circle between animate and inanimate sources¹⁷.

CARRIAGE AND OVERGROWTH: CRUCIAL EVENTS IN THE EMERGENCE OF ANTIMICROBIAL RESISTANCE

Carriage of resistant micro-organisms on admission to the ICU is to be distinguished from the carrier state of resistant micro-organisms developing during ICU stay.

Recent data from both adult and paediatric ICUs^{7,22-24} are consistent with the model in which the resistant organism identified in patients during their ICU stay are the same as harboured as part of their admission flora. Up to one third of ICU patients requiring long term intensive care and who were identified as carriers of resistant micro-organisms during their stay, brought the resistant strain into the unit. The carrier state was detected within 24hr of admission and there was no apparent association with the ICU bacterial ecology.

The obvious example is MRSA. The evolution of the resistance to methicillin amongst *S.aureus* has been claimed to be an extremely rare event²⁹. In other words, a methicillin sensitive *S.aureus* is unlikely to become resistant to methicillin during flucloxacillin therapy in ICU. It is poor management³⁰ and faecal MRSA carriage that are thought to be responsible for the high endemicity and prevalence of this micro-organism²⁶. MRSA in which resistance is associated with alterations of penicillin-binding-protein target sites²⁹ is an epidemiological marker reflecting the level of hygiene rather than the virulence of the micro-organism. Although resistant *P.aeruginosa* emerging after aminoglycoside therapy in patients who had prior carriage

of sensitive strains of the same sero-type^{31,32} has been reported, import of AGNB resistant to aminoglycosides is the common experience. Inactivating enzymes and reduced permeability and uptake have been shown to be the main mechanism of resistance in this group of antimicrobials³³.

The severity of underlying disease in critically ill ICU patients directly leads to changes in the gut mucosal defence and to impaired gut motility or ileus³⁴. Lack of peristalsis is associated with dysfunction of important physiological functions including absorption and reabsorption via the enterohepatic circulation. Serious underlying disease often includes gastric exocrine failure which contributes to the elevation of the gastric pH to >4 ³⁵. Most AGNB are effectively controlled by the physiological stomach barrier of $\text{pH} < 2$ ³⁶. Although the incidence of stress ulcer bleeding has substantially decreased over the last decade, agents which claim to confer gut protection are still administered to a large proportion of critically ill patients. Some gut protective agents such as H_2 antagonists have been claimed to increase the gastric pH, up to 8³⁷. The need for ventilation often requires opiates that further reduces gut motility. The highly concentrated normal indigenous flora, mainly anaerobic, plays a role in the control of aerobic PPM³⁸. In general, the anaerobes outnumber the aerobes by 10,000:1. Suppression of the indigenous normal flora is known to disturb this physiological balance or microbial ecology and to promote overgrowth of yeasts. High yeast levels in saliva and faeces may become clinically overt when the patient develops thrush or candidiasis of the vagina and/or groins^{39,40}. We are firmly of the opinion that although a substantial number of ICU patients have generalised inflammation but are not actually infected, most receive unnecessary, prolonged courses of antibiotic. Of course we agree that withholding antimicrobials is not an option for controlling antimicrobial usage in these specialised environments. Novel potent antimicrobials including beta-lactams combined with beta-lactamase inhibitors⁴¹ and carbapenems⁴² have anti-anaerobic activity. These newer agents reach high faecal levels due to the impaired enterohepatic circulation that in health guarantees reabsorption of most antimicrobials and therefore have a major impact on normal flora. The imbalance between the normal indigenous low pathogenic flora and the abnormal PPM is often followed by overgrowth not only of yeasts, but of enterococci and AGNB^{12,38}. Digestive tract overgrowth defined as $\geq 10^5$ potential pathogens per millilitre of saliva, gastric fluid or faeces is nearly always present in the critically ill ICU patients who require intensive care for more than three days. Overgrowth can be distinguished from low grade carriage, ie $< 10^5$ potential pathogens per millilitre or gram of digestive tract secretions, on three grounds. Firstly, digestive tract overgrowth in both oropharynx and gut is required for colonisation and infection of other internal organs¹¹. Secondly, the higher the level of carriage of PPM in both throat and/or gut, the greater the chance of transmission of the same PPM via hands of health care professionals^{9,10}. Thirdly, overgrowth is a prerequisite for the presence of a resistant mutant micro-organism within the bacterial population^{8,43}.

WHERE DOES ANTIMICROBIAL RESISTANCE EMERGE IN THE ICU PATIENT?—THE GUT

There is no evidence that resistant strains commonly emerge in internal organs such as bladder, lower airways, and blood. The combination of bactericidal antimicrobial concentrations achieved in urine, lower airway secretions and blood together with the leucocytes mobilised to fight colonisation/infection of these organs practically always guarantees the clearance of these micro-organisms and subsequent sterility. Bladder, blood and even lower airways are sterile within three days following the administration of an appropriate parenteral antimicrobial^{44,45}. However, almost all antimicrobials—apart from sterilising internal organs—are excreted via saliva, bile and mucus into the alimentary canal, in particular, into the oropharynx and gastro-intestinal canal. The antimicrobial concentrations reached in the oropharynx and gut are in general non-lethal and fluctuating, in the absence of the killing activity of salivary and faecal leucocytes. These are ideal conditions for the emergence of resistant mutant strain carried by the long-stay patient with overgrowth and subsequent carriage in high concentrations.

The classical example of the gut being the prime body site of development of resistance are the AGNB producing beta-lactamases aiming at the hydrolysis of the beta-lactam-ring in penicillins and cephalosporins^{25,43}. The use of later generation cephalosporins has been accompanied by increasing prevalence of resistance among AGNB. Resistance resulting from expression of high levels of various beta-lactamases and/or production of mutant enzymes such as extended-spectrum beta-lactamases and inhibitor-resistant TEM beta-lactamases has become problematic in many ICUs where later generation cephalosporins have been used. A correlation has been shown between the systemic administration of cefuroxime and cefotaxime and the emergence of resistant *Enterobacter* species in the gut, although the surveillance and diagnostic samples showed *Enterobacter* strains sensitive to both cephalosporins only a few days before antibiotic usage⁴³. The inducible chromosomal derepression is thought to occur in the most favourable conditions of gut overgrowth combined with non-lethal antibiotic levels in the absence of faecal leucocytes.

The reason that there are no systemic antimicrobials available that eradicate *Pseudomonas* carriage from throat and gut is that even the newest antimicrobial agents eg fluoroquinolones and carbapenems rarely reach lethal antibiotic concentrations in saliva and faeces¹⁸.

The emergence of resistance to fluoroquinolones amongst AGNB including *E.coli*, *Klebsiella*, *Enterobacter*, *Acinetobacter* and *Pseudomonas aeruginosa* is due to selection of resistant mutant strains showing alteration in their DNA-gyrase targets or changes in cellular permeability to these agents^{46,47}. The observed alterations in outer membrane proteins is thought to be associated with diminished permeability of

the *Acinetobacter* and *Pseudomonas* outer membrane proteins is thought to be associated with diminished permeability of the *Acinetobacter* and *Pseudomonas* outer membrane to the carbapenems^{48, 49}.

It is speculated that VRE may have risen to prominence since the widespread use of fluoroquinolones. These agents are often associated with the eradication of faecal carriage of sensitive AGNB¹⁸. The subsequent creation of an ecological niche may lead to enterococcal overgrowth, in particular in ICU patients with impaired motility⁵⁰. This type of patient often suffers generalised inflammation with all culture samples being negative. A popular combination of antibiotics often used in this type of ICU patient is ciprofloxacin and vancomycin as a "broad" cover for Gram negative and positive micro-organisms. The systemic vancomycin also reaches the gut via bile in non-lethal fluctuating concentrations and may select mutant VRE. In contrast, VRE has never been reported during the many decades of *C.difficile* therapy using oral vancomycin that guarantees "overkill" because of high faecal MBCs. There was no VRE detected in the most recent large *C.difficile* outbreak in North Manchester, UK despite copious administration of oral vancomycin⁵¹.

Only regular surveillance samples of throat and rectum enables the intensivist to distinguish between low-grade carriage and overgrowth in the ICU patient both on admission and during the ICU stay. We believe that the availability of the data obtained from surveillance cultures is indispensable in order to run an intensive care. The intensivist needs to know which patients carry multi-resistant AGNB, MRSA and/or VRE. The carriers represent the iceberg underneath the water surface; infected patients are only the tip of the problem.

BREACHES OF HYGIENE: TRANSMISSION VIA HANDS OF STAFF

In the enclosed environment of the ICU all types of micro-organisms whether they are low, high level pathogens or potential pathogens, aerobes or anaerobes, AGNB, methicillin-sensitive *Staphylococcus aureus* [MSSA], MRSA, yeasts, enterococci or coagulase negative staphylococci [CNS] they are all without exception transmitted from one long stay patient to another, mainly via hands of personnel including "sterile" professors and doctors, and "dirty" sisters, nurses and junior staff⁵². Health care providers are considered to be the main vehicle for the transmission of micro-organisms from one long stay ICU patient to another. Long stay patients are the main sources of the spreading of microbes. Body substances such as saliva and stool from critically ill patients contain high concentrations of micro-organisms [$10 > 8$ CFU/ml or gram]. After caring for a critically ill patient who suffers from overgrowth in throat and gut, the contamination level on the hands of the health care providers often exceeds 10^6 CFU/cm² of finger surface area. Hand washing with 0.5 per cent chlorhexidine in 70 per cent alcohol effectively clears micro-organisms from hands but only if the contamination level is $< 10^4$ CFU²⁸. In addition, a factor that has been repeatedly identified as an independent risk factor for transmission of micro-organisms is faecal carriage. There is no debate over the gut being the prime body site from where dissemination of AGNB⁵³, VRE⁵⁴, anaerobes such as *C.difficile*⁵⁵ occurs. That concept of perineal spreading was generally accepted for methicillin-sensitive *Staphylococcus aureus* [MSSA]⁵⁶, about four decades ago. Data are available supporting the concept that MRSA in terms of carriage pattern and transmissibility²⁶. Some people believe that persistence of MRSA gut carriage may explain the endemicity of MRSA in hospitals. Topical mupirocin in the nose has never been shown to clear faecal MRSA carriage⁵⁷.

These important observations may contribute to the understanding that breaches of hygiene may still occur in a busy ICU because transmission cannot be completely prevented but only reduced. However, the substantial pneumonia rate of 30 per cent in a recent prevalence study⁵⁸ suggests how naive it is to expect that the only manoeuvre of strict adherence to hand washing may control lower airway infection in the ICU⁵⁹.

THE ICU PATIENT AT RISK

Severity of underlying disease has been identified as the most important independent risk factor for acquisition and subsequent development of the carrier state of multi-resistant AGNB. Recently, scoring methods including the simplified acute physiology score (SAPS), the acute physiology and chronic health evaluation score (APACHE II) and paediatric risk and mortality score (PRISM) have become routine in teaching hospitals to estimate the degree of severity of underlying disease. A study in adult ICU patients reported that one third of the population with a mean of 13 ± 4.6 SAPS score carried multi-resistant *A. baumannii* and *K. pneumoniae* in the oropharynx and/or gut⁶⁰. Infection on admission and a high SAPS (12.3 ± 5.3) and APACHE II (20.6 ± 9.1) score were identified as independent risk factors for rectal carriage of *A. baumannii*⁶¹. In another study of ICU patients, duration of mechanical ventilation was shown to be significantly associated with faecal carriage of ESBL-producing *K. pneumoniae*⁶². A PRISM score of 6.46 ± 4.85 predicted carriage of ceftazidime-resistant micro-organisms in a paediatric ICU⁷. Invasive devices, systemic antimicrobial therapy, the presence of infection on admission, total parenteral nutrition, and the length of ICU stay are all thought to be factors that reflect severity of underlying disease. It is obvious that the more ill the ICU patient is, the higher the chance of developing a carrier state with multi-resistant micro-organisms which eventually will lead to infection of the lower airways, blood, urinary tract and wounds. The above mentioned study⁶¹ showed that the patients who developed an infection with the multi-resistant *A. baumannii* were significantly more critically ill compared with the ones who only showed the carrier state (APACHE II 26.7 ± 9.1 versus 17.7 ± 9.2 , $p < 0.05$).

Numerous studies have demonstrated a relationship between recent in-hospital antibiotic exposure and emergence of antibiotic resistance. However, virtually all of these studies differed in design. Several studies correlated the prevalence of antibiotic resistance with the degree of institution-wide antibiotic use over time^{32,63}. These studies did not include controls and other elements of care that may have influenced the frequency rate of antimicrobial resistance were not explored. Moreover, in those investigations in which control groups were defined, most studies did not perform multi-variate analyses to test for the independent effects of antibiotic exposure and other factors covariate with antibiotic use^{64,65}. Many studies identified cases through the clinical microbiology laboratory rather than prospective, scheduled culturing of all subjects so that the risk of carriage with resistant AGNB, and the size of the asymptomatic reservoir, could not be accurately defined^{32,63-66}. Several studies were conducted during epidemic conditions, when risk factors, in-hospital reservoirs, and the likelihood of person-to-person transmission are almost certainly significantly different than during endemic periods⁶³⁻⁶⁶. Finally, some studies concentrated exclusively on bacterial species known to harbour antibiotic-inducible extended spectrum chromosomal cephalosporinases^{64,66}. This selection may have strengthened the association of prior cephalosporin exposure and emergence of resistance among those species. Similarly, antibiotics have been identified as risk factors for acquiring MRSA, although recent data suggest that this might have been overestimated due to prolonged lengths of stay acting as a collinear confounding factor⁶⁷. It is obvious that the antibiotic usage will be higher in the more critically ill patients who require long-term intensive care. Apart from a marker of severity of underlying disease, antibiotics may exert a selection pressure associated with a shift towards more resistant micro-organisms. Amongst the antimicrobials, these agents that impair colonisation resistance^{12,38} may promote overgrowth enhancing the presence of mutant strains, promoting transmission and subsequent superinfection. These observations suggest that an antibiotic policy with minimal impact on the ecology may have additional beneficial effects^{12,68}. However, strict antibiotic policies will not influence the import of resistant strains carried by the patient on admission. Antibiotic policies will need to be coupled with other strategies to diminish the reservoir of carriers of resistant strains in the ICU. Oral non-absorbable antimicrobials (ie SDD), surveillance samples and a high standard of hygiene (Table 1) will likely be necessary components of this effort.

MAJOR DIFFERENCES BETWEEN THE NEW APPROACH AND THE TRADITIONAL MANAGEMENT OF RESISTANCE

The first fundamental difference between the two approaches is that routine surveillance of the carrier state enables the intensivist to be constantly aware of the organisms carried in his patient population and of the import of any new bacterium with every new admission [Table 1]. For instance, it is impossible to control MRSA without knowing the actual number of patients admitted with the organism. As isolation and barrier nursing is not routinely performed for every admission, the patients have to develop symptoms before a diagnostic sample is taken during which time there has been ample opportunity to transmit MRSA to other patients.⁶⁴

The second major difference between the two philosophies is that the traditional strategy relies upon the sole use of parenteral agents¹⁻⁴. The use of systemic agents alone is associated with the emergence of resistant strains in the gut. Whereas by combining oral topical agents with systemic agents resistant mutant strains have been effectively eradicated^{13,14,16}.

Finally, disturbance of the gut ecology results in overgrowth of multi-resistant micro-organisms. In general, the broader the spectrum of antimicrobials, the greater the impact on the ecology of gut flora^{41,42}. Antimicrobials that spare the gut ecology to a greater extent are still effective when combined with SDD.

TRADITIONAL APPROACH: HAND WASHING DOES NOT EFFECT THE CARRIER STATE

Hand washing with disinfecting agents has been the cornerstone of infection control in ICU [Table 1]. The inherent limitation of the intervention of handwashing is the inability to clear carriage of [multi-resistant] micro-organisms. Hence, the substantial import of resistance will not be affected by strict adherence to handwashing. The rationale for this traditional cornerstone is that the manoeuvre of hand washing is generally accepted to be effective in controlling transmission of micro-organisms^{59,70}. However, *in-vitro* work shows that the efficacy of hand washing is dependent on the level of hand contamination²⁸ which again is determined by the level of carriage in throat and/or gut. *In-vivo* data showing the complete prevention of PPM transmission are lacking^{28,71}. Although it is recognised by opinion leaders that handwashing compliance is very poor, hand washing is still the only manoeuvre highly recommended by influential authorities including the CDC⁷². Remarkable is the reluctance to look at other interventions to control multi-resistant micro-organisms amongst the same opinion leaders despite the non-compliance with their golden rule. Hence, because of [i] the inability to control import of resistance; [ii] the partial efficacy of handwashing to prevent transmission; and [iii] the recognised failure to ensure handwashing, under the traditional policy transmission of resistant micro-organisms from one long stay ICU patient who is a faecal carrier to another ICU patient is theoretically impossible to prevent. There are no randomised trials showing that significantly less ICU patients die when health care workers adhere to hand washing practices. Pneumonia reduction has never been shown following the implementation of hand washing⁷³.

NOVEL APPROACH: SDD PREVENTS OR ERADICATES, IF INITIALLY PRESENT, THE CARRIER STATE

If it is impossible to improve the record of the traditional approach, the evaluation of alternative interventions is perfectly justified (Table 1). Why not monitoring the magnitude of the source of resistant micro-organisms, ie, the numbers of carriers in the enclosed environment of the ICU? Especially now, as there are new methods available to eradicate the carrier state of multi-resistant organisms. A promising approach to control the emergence and spread of resistant micro-organisms, the restoration of the microbial ecological balance, is not often given much consideration, but may turn out to be a prerequisite in the future fight against resistance.

1. *Surveillance cultures of throat/rectum*

The first step in the control of multi-resistant micro-organisms in the ICU should be the introduction of *surveillance cultures* of throat and rectum. These samples do not need to be obtained from the whole ICU population, only the subset of patients who may have a chance of developing a secondary endogenous or exogenous infection, ie, the homogeneous group of ICU patients who require minimal three days of ventilation due to severity of underlying disease. Patients who are that ill that they are expected to stay more than three days, with a PRISM score of ≥ 12 or APACHE score of ≥ 14 require surveillance sampling on admission, and twice weekly (Monday, Thursday) afterwards. Screening for carriers of multi-resistant micro-organisms, rather than simply identifying infected patients has a major role in the control of an outbreak, and reduces the number of infected patients. Although detecting multi-resistant micro-organisms in routine clinical specimens provides important information, many studies show this to be inadequate⁷⁴. Surveillance cultures have three endpoints: (a) to distinguish infections of exogenous pathogenesis (ie, without previous carriage) from primary and secondary endogenous infections; for example, surveillance cultures of throat and rectum are perceived to be the only manoeuvre that enables the distinction between animate versus inanimate sources; (b) to detect the carrier of multi-resistant micro-organisms on admission and throughout ICU stay; and (c) to evaluate the efficacy of oral non-absorbable antibiotics for treatment of carriage of multi-resistant bacteria.

2. *When to treat carriers with oral non-absorbable antimicrobials*

There are three different approaches.

- (i) SDD with polymyxin/tobramycin is implemented as a routine infection prophylaxis in patients requiring minimally three days of ventilation and showing overgrowth with AGNB, yeasts and *S.aureus*. It is very unlikely that resistance against systemic antibiotics will develop in patients who are successfully decontaminated, ie, who do not carry AGNB, yeasts and *S.aureus*. This approach aims at the prevention of development of resistance towards the systemic antimicrobials used in the ICU^{13, 14, 75}.
- (ii) SDD is started as soon as one patient carries a resistant micro-organism. The aim is to prevent transmission of the resistant strains, before infections occur in the unit⁷⁶.
- (iii) Only when diagnostic samples reveal that a patient is infected with resistant AGNB or MRSA, SDD is administered to all carriers both symptomatic and non-symptomatic^{9, 10, 19}.

Overgrowth of both sensitive and resistant AGNB can be eradicated with the combination polymyxin/tobramycin¹⁴, whilst vancomycin is found to be effective in clearing MRSA carriage⁷⁷. For example, SDD applied in the correct manner effectively controlled recent outbreaks due to multi-resistant *P.aeruginosa* and *Acinetobacter baumannii*. Both AGNB were sensitive to polymyxin E ($<0.5\text{mg/L}$) and showed only reduced sensitivity to tobramycin (4mg/L). Carriage was effectively cleared following the high concentrations achieved in saliva and faeces (up to 100mg/kg) of the synergistic mixture of polymyxin E and tobramycin (0.125mg/L and 2mg/L), respectively. Even the vancomycin resistant MRSA with an MBC of 8mg/L is unlikely to survive in gut concentrations of up to 1800mg/kg following the oral administration of vancomycin doses used for *C.difficile* eradication. The manoeuvre of hand washing is perceived to be more effective in an ICU where long stay patients are successfully decontaminated, ie, in the absence of sources of resistant PPM. We believe that VRE is a low level pathogen, compared with AGNB and *S.aureus*. Recent data show that there is no difference in morbidity and mortality in patients with a septicaemia due to enterococci sensitive or resistant to vancomycin^{78, 79}. VRE carriage does not need oral non-absorbable antimicrobials⁸⁰. A prudent antibiotic policy with ecology sparing antibiotics for short courses combined with proper infection control may be more beneficial⁶ (Table 2).

3. *Preservation of the microbial ecology*

Microbial ecology is the physiological concept that the patient's indigenous flora, mainly anaerobes, provide resistance to PPM (ie, colonisation resistance)^{12, 38}. The most profound disruption of colonisation resistance has been seen with late cephalosporins such as ceftriaxone¹², beta-lactams combined with beta-lactamase inhibitors⁴¹ and carbapenems⁴². This leads directly to digestive tract overgrowth a recognised risk factor for emergence of resistance, transmission and superinfection. In general, the impact of early

7. Toltzis P, Yamashita T, Vilt L et al. Colonization with antibiotic-resistant Gram-negative organisms in a pediatric intensive care unit. *Crit Care Med* 1997; 25: 538-544.
8. Hiramatsu K, Aritaka N, Hanaki H et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *Lancet* 1997; 350: 1670-1673.
9. Brun-Buisson C, Legrand P, Rauss A et al. Intestinal decontamination for control of nosocomial multiresistant Gram-negative bacilli. *Ann Intern Med* 1989; 110: 873-881.
10. Bonten MJM, Gaillard CA, Johanson WG et al. Colonization in patients receiving and not receiving topical antimicrobial prophylaxis. *Am J Respir Crit Care Med* 1994; 150: 1332-1340.
11. van Uffelen R, van Saene HKF, Fidler V et al. Oropharyngeal flora as a source of bacteria colonizing the lower airways in patients on artificial ventilation. *Intensive Care Med* 1984; 10: 233-237.
12. Eickhoff TC. Antibiotics and nosocomial infections. In: Hospital Infections. Eds Bennett JV, Brachman PS. Little, Brown and Company, Boston 1992 3rd edit. pp 245-264.
13. Brun-Buisson C, van Saene HKF. SDD and the novel extended-broad-spectrum beta-lactamases. *J Antimicrob Chemother* 1991; 28: 145-147.
14. Baxby D, van Saene HKF, Stoutenbeek CP et al. Selective decontamination of the digestive tract: 13 years on, what it is and what it is not. *Intensive Care Med* 1996; 22: 699-706.
15. van Saene HKF, Silvestri L, Baines P. Definitions. In: Infection Control in the intensive care unit. Eds HKF van Saene, L Silvestri, MA de la Cal. Springer-Verlag Italia, Milano, 1998; 1st ed: pp1-8.
16. van Saene HKF, Stoutenbeek CP, Hart CA. Selective decontamination of the digestive tract [SDD] in intensive care patients: a critical evaluation of the clinical, bacteriological and epidemiological benefits. *J Hosp Infect* 1991; 18: 261-277.
17. Damjanovic V, van Saene HKF. Outbreaks of infection in neonatal intensive care units [NICU]. *J Hosp Infect* 1997; 35: 237-242.
18. van Saene HKF, Percival A. Bowel micro-organisms—a target for selective antimicrobial control. *J Hosp Infect* 1991; 19: [Suppl C]: 19-41.
19. Taylor ME, Oppenheim BA. Selective decontamination of the gastrointestinal tract as an infection control measure. *J Hosp Infect* 1991; 17: 271-278.
20. Maki DG, Alvarado CJ, Hassemer CA et al. Relation of the inanimate hospital environment to endemic nosocomial infection. *New Engl J Med* 1982; 307: 1562-1566.
21. Levin MH, Olsen B, Nathan C et al. *Pseudomonas* in the sinks of an intensive care unit: relation to patients. *J Clin Pathol* 1984; 37: 424-427.
22. Berkowitz FE, Metchock B. Third generation cephalosporin-resistant Gram-negative bacilli in the faeces of hospitalized children. *Pediatr Infect Dis J* 1995; 14: 97-100.
23. Olsen B, Weinstein RA, Nathan C et al. Epidemiology of endemic *Pseudomonas aeruginosa*: why infection control measures have failed. *J Infect Dis* 1984; 6: 808-816.
24. Flynn DM, Weinstein RA, Nathan C et al. Patients' endogenous flora as the source of "nosocomial" *Enterobacter* in cardiac surgery. *J Infect Dis* 1987; 156: 363-368.
25. Weinstein RA. Endemic emergence of cephalosporin-resistant *Enterobacter*: relation to prior therapy. *Infection Control* 1986; 7: 120-123.
26. Rimland D, Robertson B. Gastro-intestinal carriage of methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol* 1986; 24: 137-138.
27. Chambers ST, Steele C, Kunin CM. Enteric colonization with antibiotic resistance bacteria in nurses working in intensive care units. *J Antimicrob Chemother* 1987; 19: 685-693.
28. Nystrom B. Optimal design/personnel for control of intensive care unit infection. *Infect Control* 1983; 4: 388-390.
29. Kreiswirth B, Kornblum J, Arbeit RD et al. Evidence for a clonal origin of methicillin resistance in *Staphylococcus aureus*. *Science* 1993; 259: 227-230.
30. Espersen F, Nielsen PB, Lund K et al. Hospital-acquired infections in a burns unit caused by an imported strain of *Staphylococcus aureus* with unusual multi-resistance. *J Hyg* 1982; 88: 535-539.
31. Weinstein RA, Nathan C, Gruensfelder R et al. Endemic aminoglycoside resistance in Gram-negative bacilli: epidemiology and mechanisms. *J Infect Dis* 1980; 141: 338-345.
32. Hammond MJM, Potgieter PD, Forder AA et al. Influence of amikacin as the primary aminoglycoside on bacterial isolates in the intensive care unit. *Crit Car Med* 1990; 18: 607-510.
33. Grayson ML, Eliopoulos GM. Antimicrobial resistance in the intensive care unit. *Seminars in Respiratory Infections* 1990; 5: 204-214.
34. Rombeau JL, Takala J. Summary of round table conference: gut dysfunction in critical illness. *Interns Care Med* 1997; 23: 476-479.

35. Stannard VA, Hutchinson A, Morris DL et al. Gastric exocrine "failure" in critically ill patients: incidence and associated features. *BMJ* 1988; 296: 155-156.
36. Giannella RA, Broitman SA, Zamcheck N. Gastric acid barrier to ingested micro-organisms in man: studies *in-vivo* and *in-vitro*. *Gut* 1972; 13: 251-256.
37. Donowitz LG, Page MC, Mileur BL et al. Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. *Infect Control* 1986; 7: 23-26.
38. Vollaard EJ, Clasener HAL. Colonization resistance. *Antimicrob Ag Chemother* 1994; 38: 409-414.
39. Miles MR, Olsen L, Rogers A. Recurrent vaginal candidiasis. Importance of an intestinal reservoir. *JAMA* 1977; 238: 1836-1837.
40. Samonis G, Gikas A, Toloudis P et al. Prospective study of the impact of broad-spectrum antibiotics on the yeast flora of the human gut. *Eur J Clin Microbiol Infect Dis* 1994; 13: 665-667.
41. Kager L, Malmberg AS, Sjöstedt S et al. Concentrations of ampicillin plus sulbactam in serum and intestinal mucosa and its effects on the colonic microflora in patients undergoing colorectal surgery. *Eur J Clin Microbiol* 1983; 2: 559-563.
42. Rolston KVI, Berkey P, Bodey GP et al. A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. *Arch Intern Med* 1992; 152: 283-291.
43. Modi N, Damjanovic V, Cooke RWI. Outbreak of cephalosporin resistant *Enterobacter cloacae* infection in a neonatal intensive care unit. *Arch Dis Child* 1987; 62: 148-151.
44. A'Court CHD, Garrard CS, Crook D et al. Microbiological lung surveillance in mechanically ventilated patients, using non-directed bronchial lavage and quantitative culture. *QJM* 1993; 86: 635-648.
45. Montravers Ph, Fagon JY, Chastre J et al. Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. *Am Rev Resp Dis* 1993; 147: 38-44.
46. Peloquin CA, Cumbo TJ, Nix DE et al. Evaluation of intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections. *Arch Intern Med* 1989; 149: 2269-2273.
47. Fink MP, Snyderman DR, Niederman MS et al. Treatment of severe pneumonia in hospitalized patients: results of a multi-centre, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. *Antimicrob Ag Chemother* 1994; 38: 547-557.
48. Go ES, Urban C, Burns J et al. Clinical and molecular epidemiology of *Acinetobacter* infections sensitive only to polymyxin B and sulbactam. *Lancet* 1994; 344: 1329-1332.
49. Quinn JP, Studemeister AE, DiVincenzo CA, Lerner SA. Resistance to imipenem in *Pseudomonas aeruginosa*: clinical experience and biochemical mechanisms. *Rev Infect Dis* 1988; 10: 892-898.
50. Zervos MJ, Bacon AE III, Patterson JE et al. Enterococcal superinfection in patients treated with ciprofloxacin. *J Antimicrob Chemother* 1988; 21: 113-115.
51. Chadwick PR, Chadwick CD, Oppenheim BA. Report of a meeting on the epidemiology and control of glycopeptide-resistant enterococci. *J Hosp Infect* 1996; 33: 83-92.
52. Gaya H. Infection control in intensive care. *Br J Anaesthesia* 1976; 48: 9-12.
53. Selden R, Lee S, Wang WL et al. Nosocomial *Klebsiella* infections: intestinal colonization as a reservoir. *Ann Intern Med* 1971; 74: 657-664.
54. Wells CL, Juni BA, Cameron SB et al. Stool carriage, clinical isolation and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. *Clin Infect Dis* 1995; 21: 45-50.
55. McFarland LV, Surawicz CM, Stamm WF. Risk factors for *Clostridium difficile* carriage and *C. difficile* associated diarrhoea in a cohort of hospitalized patients. *J Infect Dis* 1990; 162: 678-684.
56. Greendyke RM, Constantine HP, Magruder GB et al. Staphylococci on a medical ward, with special reference to faecal carriers. *Am J Clin Pathol* 1958; 30: 318-322.
57. Dacre J, Emmerson AM, Jenner EA. Gentamicin-methicillin-resistant *Staphylococcus aureus*: epidemiology and containment of an outbreak. *J Hosp Infect* 1986; 7: 134-136.
58. Vincent JL, Bihari DJ, Suter PM et al. The prevalence of nosocomial infection in intensive care units in Europe. *JAMA* 1995; 274: 639-644.
59. Jarvis WR. Handwashing—the Semmelweis lesson forgotten? *Lancet* 1994; 344: 1311-1312.
60. Garrouste-Orgeas M, Marie O, Rouveau M et al. Secondary carriage with multi-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* in an adult ICU population: relationship with nosocomial infections and mortality. *J Hosp Infect* 1996; 34: 279-289.
61. Lortholary O, Fagon JY, Hoi AB et al. Nosocomial acquisition of multi-resistant *Acinetobacter baumannii*: Risk factors and prognosis. *Clin Infect Dis* 1995; 20: 790-796.
62. Pena C, Pujol M, Ricart A et al. Risk factors for faecal carriage of *Klebsiella pneumoniae* producing extended spectrum beta-lactamase [ESBL-KP] in the ICU. *J Hosp Infect* 1997; 35: 9-16.

63. Meyer KS, Urban C, Eapan JA et al. Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. *Ann Intern Med* 1993; 119: 353-358.
64. Chow JW, Fine MJ, Shlaes DM et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; 115: 585-590.
65. Tullus K, Berglund B, Burman LG. Emergence of cross-resistance to β -lactam antibiotics in faecal *Escherichia coli* and *Klebsiella* strains from neonates treated with ampicillin or cefuroxime. *Antimicrob Ag Chemother* 1990; 34: 361-362.
66. Jacobson KL, Cohen SH, Inciardi JF et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I β -lactamase-producing organisms. *Clin Infect Dis* 1995; 21: 1107-1113.
67. Asensio A, Guerrero A, Querida C et al. Colonization and infection with methicillin-resistant *S. aureus*: associated factors and eradication. *Infect Control Hosp Epidemiol* 1996; 17: 20-28.
68. van Saene HKF, Willems FTC, Davies RJ. The abnormal carrier state and superinfection following antibiotic treatment of respiratory tract infection in general practice: A clinical controlled trial. *Eur Respir Rev* 1992; 2: 193-198.
69. Patterson JE. Making real sense of MRSA. *Lancet* 1996; 348: 836-837.
70. Larson E. A casual link between handwashing and risk of infection? Examination of the evidence. *Infect Control Hosp Epidemiol* 1988; 9: 28-36.
71. Larson EL. Persistent carriage of Gram-negative bacteria on hands. *Am J Infect Control* 1981; 9: 112-119.
72. Goldmann D, Larson E. Handwashing and nosocomial infections. *New Engl J Med* 1992; 327: 120-122.
73. Daschner FD, Frey D, Wolff G et al. Nosocomial infections in intensive care wards. A multicenter prospective study. *Intensive Care Med* 1982; 8: 5-9.
74. Cookson B. Is it time to stop searching for MRSA? Screening is still important. *BMJ* 1997; 14: 664-666.
75. Hammond JMJ, Potgieter PD. Long-term effects of selective decontamination on antimicrobial resistance. *Crit Care Med* 1995; 23: 637-645.
76. Weinstein RA, Kabins SK. Strategies for prevention and control of multiple drug-resistant nosocomial infection. *Am J Med* 1981; 70: 449-454.
77. de la Cal MA, Garcia-Hierro P, Cerda E et al. Primary endogenous pneumonia is associated with mortality in severe burns. *Ann Surg* 1998; submitted.
78. Quale J, Landman D, Alwood E et al. Experience with a hospital-wide outbreak of vancomycin-resistant enterococci. *Am J Infect Control* 1996; 24: 372-379.
79. Mainous MR, Lipsett PA, O'Brien M et al. Enterococcal bacteraemia in the surgical intensive care unit. *Arch Surg* 1997; 132: 76-81.
80. Quale J, Landman D, Suarina G et al. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. *Clin Infect Dis* 1996; 23: 1020-1025.
81. Vollaard EJ, Clasener HAL, Janssen AJHM. Influence of cephadrine on microbial colonization resistance in healthy volunteers. *Microb Ecol Health Dis* 1992; 5: 147-153.
82. van Saene HKF, Stoutenbeek CP, Geitz JN et al. Effect of amoxycillin on colonization resistance in human volunteers. *Microb Ecol Health Dis* 1988; 1: 169-177.
83. Vlasplolder F, de Zeeuw G, Rozenberg-Arska M et al. The influence of flucloxacillin and amoxicillin with clavulanic acid on the aerobic flora of the alimentary canal. *Infection* 1987; 15: 241-244.
84. Selwyn S. Microbiological and clinical implications of the pharmacokinetics of cephalosporins. In: New Criteria for Antimicrobial Therapy: Maintenance of Digestive Tract Colonization Resistance. Eds D van der Waaij, J Verhoef. Excerpta Medica, Amsterdam, 1979; 147-157.
85. Witte W, Kresken M, Bräulke C et al. Increasing incidence and wide spread dissemination of methicillin-resistant *Staphylococcus aureus* [MRSA] in hospitals in central Europe, with special reference to German hospitals. *Clin Microb Infect* 1997; 3: 414-422.
86. Sprunt K. Practical use of surveillance for prevention of nosocomial infection. *Seminars in Perinatology* 1985; 9: 47-50.
87. Pierro A, van Saene HKF, Jones MO et al. Clinical impact of abnormal gut flora in infants receiving parenteral nutrition. *Ann Surg* 1998; in press.

Table 1

DIFFERENCES BETWEEN THE CONVENTIONAL APPROACH TO RESISTANCE WHICH IS MICRO-ORGANISM RELATED AND THE NEW APPROACH WHICH IS PATIENT DIRECTED

<i>Traditional approach based upon in vitro data</i>	<i>New approach based upon pathogenesis</i>
Micro-organism related approach	Patient directed approach
Diagnostic samples used to confirm a microbiological cause of inflammation	Diagnostic samples and surveillance samples to detect infected patients and asymptomatic carriers
Diagnostic samples are only taken when clinically indicated ie when macroscopically lower airway secretion and urine are turbid	Surveillance samples are taken on admission and twice weekly thereafter in subsets of patients identified by PRISM > 12; APACHE > 14; > 3d ICU stay
A carrier admitted to the ICU can remain undetected until an infection develops	Carriers of resistant organisms imported into the ICU are readily detected when surveillance is routinely performed on admission
There is an inherent delay in recognising the presence of a patient with a resistant strain	With constant surveillance both carriers and infected cases are detected early
The exclusive use of parenteral antibiotics has the inherent risk of emergence of resistant mutants in the gut	Parenteral antibiotics combined with SDD has minimal risk of mutants emerging in the gut
New agents are constantly required to replace older antibiotics	The combined use of SDD and systemic agents keeps the parenteral agents effective
Newer and potent agents disrupt the gut ecology and promotes overgrowth	Older agents still useful leaving the gut ecology relatively undisturbed
Control of transmission of resistant microorganisms sought	Clearance of the carrier state sought
High standards of hygiene needed including hand washing, gloves, gowns, masks and barrier nursing	Only following elimination of the carrier state can these traditional methods become more effective
Use of oral topical antibiotics discouraged, ignoring available evidence	Use of oral topical agents in the attempt to control resistance is evidence based

Table 2

IMPORTANT FEATURES OF PROGRAM FOR PREVENTING ANTIMICROBIAL RESISTANCE IN ICU

1. *surveillance cultures of throat and rectum* to detect transmission/overgrowth
to detect carriers of multi-resistant strains on admission and afterwards twice weekly
2. *rigid enforcement of infection control procedures* to prevent transmission
a. unannounced inspections for compliance;
b. sanctions for repeated failure to comply
3. *a prudent use of systemic antimicrobials* to discourage overgrowth
a. avoidance of unnecessary antibiotic therapy;
b. use of the shortest possible duration of systemic antibiotic treatment: 5 days followed by clinical, haematological and microbiological re-evaluation;
c. avoidance of new potent antimicrobials that suppress the indigenous flora, ie that have anti-anaerobic activity and that are excreted via the biliary tract (except when necessary)
4. *oral non-absorbable antimicrobials* to prevent/eradicate overgrowth
AGNB: polymyxin/tobramycin^o oral/topical
MRSA: vancomycin^o oral/topical
YEAST: polyenes^o oral/topical
VRE: traditional control measures, and reconsider use of older antimicrobials

Memorandum by the Scottish Office**PUBLIC HEALTH-RELATED LABORATORY SERVICES IN SCOTLAND**

In Scotland the necessary microbiological service for public health is provided by a network of Health Boards (equivalent to Health Authorities in England and Wales) and university laboratories. In addition, The Scottish Office funds directly a group of reference laboratories which deal with organisms of major public health significance, ie salmonella, campylobacter, E.coli 0157, MRSA and meningococcal bacteria. Health Board and university laboratories in Scotland also use in some circumstances, eg influenza, the services of the Central Public Health Laboratory, Colindale.

The Common Services Agency for the National Health Service in Scotland provides a number of centrally-administered services. Among these are the Information and Statistics Division, which collates and analyses health service-related data for Scotland and publishes an annual summary of returns of notifiable diseases and therefore performs a function equivalent to that of the Office of National Statistics in England and Wales. Another division of the Common Services Agency, The Scottish Centre for Infection and Environmental Health (SCIEH) undertakes surveillance of infection, co-ordination of relevant agencies in the investigation and control of infection, disseminates information about infection, advises The Scottish Office on infection problems and provides education and training. SCIEH also carries out epidemiological analysis of communicable disease statistics, and across the range of its functions is broadly analogous to the Communicable Disease Surveillance Centre for England and Wales.

Since 1967 all NHS, reference and university microbiology laboratories in Scotland have voluntarily reported laboratory-diagnosed infections to The Scottish Centre for Infection and Environmental Health. While this resembles the position in England and Wales, there is evidence that reporting may be more comprehensive in Scotland, despite the fact that the Scottish Centre has no organisational relationship with any of the laboratories, unlike in England and Wales where The Communicable Disease Surveillance Centre is an integral part of the PHLS. SCIEH does however have close links with Scottish laboratories. The laboratory reporting system was strengthened in 1989 by the designation of 30 infections, which, while distinct from the statutorily notifiable diseases, were and are considered to be sufficiently important to justify reporting to SCIEH. While, in practice, the laboratories make the majority of these reports, environmental health officers, consultants in public health medicine, nurses and clinicians are encouraged to report these infections to SCIEH. As in England and Wales, information on outbreaks of disease is reported to SCIEH by consultants in public health medicine, microbiologists, consultant physicians in infectious diseases, and environmental health officers. This is similar to the position in England and Wales.

In response to a recommendation in the Pennington Report on the circumstances leading to the 1996 outbreak of infection with E.coli 0157 in central Scotland, work is in progress towards establishing an electronic laboratory reporting system which will allow for the rapid transfer of information from laboratories to SCIEH, general practitioners, consultants in public health medicine and local authorities. It is expected this system will be fully compatible with that already in place in the PHLS.

The efficiency and effectiveness of these arrangements are kept under review. In the course of a recent review of the Scottish reference laboratories it was concluded that for reasons of clinical effectiveness (in particular, the speed with which samples can be taken to laboratories, which is important in outbreak control) and cost effectiveness, it was preferable that the work done by these laboratories should continue to be done in Scotland rather than by the PHLS in England and Wales.

16 February 1998

Note by the Veterinary Medicines Directorate**PROCEDURE FOR REMOVING ADDITIVES FROM
THE ANNEXES OF DIRECTIVE 70/524/EEC****BACKGROUND**

1. Additives in animal feeding stuffs are controlled throughout the EU under Council Directive 70/524/EEC. This provides that no additive may be used in animal feed unless it is approved by Community procedure, including a requirement that, at the level permitted in feedingstuffs, it does not adversely affect human or animal health or the environment. A Community authorised additive may be freely marketed in the European Union in accordance with Directive 70/524/EEC as amended.

APPROVALS

2. Approved additives are currently listed as active ingredients in Annexes to the Directive. The Annexes set down conditions of use such as species, age of animal and maximum and minimum content in feed. Directive 96/51/EC, part of which is due to be implemented in the UK on 1 April 1998, will require the approval of zootechnical additives (eg antibiotics, growth promoters) to be linked to the person responsible for marketing.

3. For an additive to obtain Community approval, a dossier of evidence satisfying the criteria of safety, quality and efficacy is submitted by the applicant, through an appointed rapporteur (in the UK, the Veterinary Medicines Directorate), to the European Commission, which consults its independent Scientific Committee on Animal Nutrition (SCAN). The opinion of SCAN is then considered in a further committee of representatives of Member States (the Standing Committee) which agrees whether or not the substance should be entered into one of the Annexes.

REMOVALS

4. Safeguard measures are set out in Article 11 of the Directive. This allows a Member State temporarily to suspend or restrict the application of the provisions of the Directive within the Member State. This may be done if the Member State has received new information or a reassessment of existing information and has detailed grounds for establishing that the use of an authorised additive, or its use in specified conditions, constitutes a danger to human or animal health or to the environment.

5. Other Member States and the Commission must be notified and scientific justification for the measures taken must be provided. The Commission consults Member States within the Standing Committee, which must deliver its opinion without delay and the Commission then take appropriate measures. If the Commission considers that amendments are necessary (these could include removal of approval) a draft of the measures to be adopted will be submitted to the Standing Committee. The Committee must deliver its opinion by qualified majority within two days. In practice, the Commission tends to consult SCAN on the evidence produced by the Member State which has implemented a unilateral ban before the Standing Committee procedure is invoked.

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